EXHIBIT 1 TO
AMENDMENT AFTER FINAL ACTION
&
WITHDRAWAL OF OCTOBER 3, 2007 PETITION TO WITHDRAW FINALITY,
TO WITHDRAW JULY 3, 2007 OFFICE ACTION, FOR INTERVIEW,
AND FOR CORRECT / PROPER OFFICE ACTIONS
&
INTERVIEW SUMMARY
&
REQUEST FOR ANY NECESSARY EXTENSION OF TIME

US006476011B1

(12) **United States Patent**
Reed et al.

(10) **Patent No.: US 6,476,011 B1**
(45) **Date of Patent: *Nov. 5, 2002**

(54) **METHODS FOR INTRODUCING AN ESTROGENIC COMPOUND**

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(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/193,970**

(22) Filed: **Nov. 18, 1998**

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/111,927, filed on Jul. 8, 1998, now Pat. No. 6,011,024, which is a continuation-in-part of application No. 08/458,352, filed on Jun. 2, 1995, now Pat. No. 5,830,886, which is a division of application No. 08/196,192, filed as application No. PCT/GB92/01587 on Aug. 28, 1992, now Pat. No. 5,616,574, application No. 09/193,970, which is a continuation-in-part of application No. 08/142,194, filed on Sep. 2, 1998, now Pat. No. 6,083,978, and a continuation-in part of application No. PCT/GB97/00600, filed on Mar. 4, 1997, application No. 09/193,970, which is a continuation-in-part of application No. 09/125,255, filed on Aug. 14, 1998, and a continuation-in-part of application No. PCT/GB97/00444, filed on Feb. 17, 1997, application No. 09/193,970, which is a continuation-in-part of application No. PCT/GB97/03352, filed on Dec. 4, 1997.

(30) **Foreign Application Priority Data**

Aug. 28, 1991 (GB) 9118478

(51) **Int. Cl.**[7] **A61K 31/56**
(52) **U.S. Cl.** **514/178**; 514/607
(58) **Field of Search** 514/178, 607

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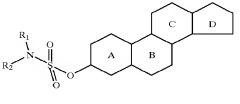
(57) **ABSTRACT**

The invention pertains to methods for introducing an estrogenic compound into a subject in need thereof involving administering an effective amount of a ring system compound having the formula (II)

(II)



wherein each of R_1 and R_2 is independently selected from H, alkyl, alkenyl, cycloalkyl and aryl, and at least one of R_1 and R_2 is H, or together represent alkylene optionally containing one or more hetero atoms or groups in the alkylene chain; and the ring system ABCD represents a substituted or unsubstituted, saturated or unsaturated steroid nucleus selected from the group consisting of oestrones, dehydroepiandrosterones, substituted oestrones, oestradiols, substituted oestradiols, oestriols, substituted dehydroepiandrosterones, or substituted oestriols; wherein the compound is an inhibitor of an enzyme having steroid sulphatase activity (EC 3,1,6,2), or a pharmceutically acceptable salt thereof.

14 Claims, 26 Drawing Sheets

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mM; 0.8 mM; 1.0 mM. After incubation each sample was cooled and the medium (1 ml) was pipetted into separate tubes containing [^{14}C]oestrone (7×10^3 dpm) (specific activity 97 Ci/mmol from Amersham International Radiochemical Centre, Amersham, U.K.). The mixture was shaken thoroughly for 30 seconds with toluene (5 ml). Experiments showed that >90% [^{14}C]oestrone and <0.1% [^{3}H]oestrone-3-sulphate was removed from the aqueous phase by his treatment. A portion (2 ml) of the organic phase was removed, evaporated and the ^{3}H and ^{14}C content of the residue determined by scintillation spectrometry. The mass of oestrone-3-sulphate hydrolysed was calculated from the ^{3}H counts obtained (corrected for the volumes of the medium and organic phase used, and for recovery of [^{14}C] oestrone added) and the specific activity of the substrate.

For the present invention, the percentage inhibition for the series of EMATE analogues tested in either MCF-7 cells or placental microsomes is shown in Table 1, below.

In Vivo Studies

Using 17-deoxy oestrone-3-O-sulphamate (NOMATE, FIG. **28**, Formula 1V where X=—OSO_2NH_2, Y=—CH_2— and R_1 and R_2=H, and FIG. **36**) as a representative example, the ability of this compound to inhibit oestrone sulphatase activity in vivo was examined in rats. The oestrogenicity of this compound was examined in ovariectomised rats. In this model compounds which are oestrogenic stimulate uterine growth.

(i) Inhibition of Oestrone Sulphatase Activity in vivo

NOMATE (0.1 mg/Kg/day for five days) was administered orally to rats with another group of animals receiving vehicle only (propylene glycol). At the end of the study samples of liver tissue were obtained and oestrone sulphatase activity assayed using ^{3}H oestrone sulphate as the substrate as previously described (Int. J. Cancer, 1995, 62, 106–11).

As shown in FIG. **39**, administration of this dose of NOMATE effectively inhibited oestrone sulphatase activity by 98% compared with untreated controls.

(ii) Lack of in vivo Oestrogenicity

NOMATE (0.1 mg/Kg/day for five days) was administered orally to rats with another group of animals receiving vehicle only (propylene glycol). At the end of the study uteri were obtained and weighed with the results being expressed as uterine weight/whole body weight×100.

As shown in FIG. **40** administration of NOMATE at the dose tested, but had no significant effect on uterine growth, showing that at this dose the compound is not oestrogenic.

TABLE 1

Inhibition of Oestrone Sulphatase Activity in MCF-7 Cells or Placental Microsomes by EMATE Analogues

	Concentration	% Inhibition (Mean)	
			Placental
Inhibitor	Tested (mM)	MCF-7 Cells	Microsomes
2-n-propyl EMATE	0.1	41.1	—
	1	83.1	21.9
	10	92.2	43.2
	25	—	47.5
	50	—	61.1
	100	—	69.2
4-n-propyl EMATA	1	13.7	
	10	—	10.2
	25	—	15.7
	50	—	16.3
	100	—	23.7

TABLE 1-continued

Inhibition of Oestrone Sulphatase Activity in MCF-7 Cells or Placental Microsomes by EMATE Analogues

	Concentration	% Inhibition (Mean)	
			Placental
Inhibitor	Tested (mM)	MCF-7 Cells	Microsomes
2,4-n-propyl EMATE	0.1	6.6	—
	1	10.6	—
2-allyl EMATE	0.01	23.2	—
	0.1	76.1	—
	1	94.2	45.6
	10	93.7	65.4
	25	—	75.3
	50	—	86.6
	100	—	89.6
4-allyl EMATE	1	—	29.1
(approx 75%)	10	—	54.2
	25	—	59.0
	50	—	65.1
	100	—	71.9
2,4-di-allyl EMATA	—	—	—
2-methoxy EMATA	0.1	96.0	—
	1	93.6	—
	10	96.2	99.0
	50	—	99.7
	100	—	99.7
2-nitro EMATE	0.05	—	44.5
	0.5	—	93.9
	5	—	99.0
	50	—	99.4
4-nitro EMATE	20	—	99.0
NOMATE	0.1	96.4	97.2
(17-deoxy EMATE)	1	99.1	99.5
	10	99.7	99.5
	25	99.7	99.7

— = not tested

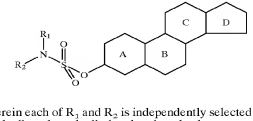
Irreversible time- and concentration-dependent assumed for these compounds in keeping with established precedent (Biochemistry, 1995, 34, 11508–11).

Other modifications of the present invention will be apparent to those skilled in the art.

What is claimed is:

1. A method for introducing an estrogenic compound into a subject in need thereof comprising administering an effective amount of a ring system compound having the formula **(II)**

(II)



wherein each of R_1 and R_2 is independently selected from H, alkyl, alkenyl, cycloalkyl and aryl; and at least one of R_1 and R_2 is H, or together represent alkylene optionally having one or more hetero atoms or groups in the alkylene chain; and the ring system ABCD represents a substituted or unsubstituted, saturated or unsaturated steroid nucleus selected from the group consisting of oestrones, dehydroepiandrosterones, substituted oestrones, oestradiols, substituted oestradiols, oestriols, substituted dehydroepiandrosterones and substituted oestriols; wherein said compound is an inhibitor of an enzyme having steroid sulphatase activity (EC 3.1.6.2), or a pharmaceutically acceptable salt thereof.

2. The method of claim **1**, wherein R_1 and R_2 are independently H or C_1–C_5 alkyl, and at least one of R_1 and R_2 is H; and the ring system ABCD represents a steroid nucleus, selected from the group consisting of dehydroepiandrosterone, oestrone, 2-OH-oestrone, 7α-OH-oestrone, 2-methoxy-oestrone, 16α-OH-oestrone, 4-OH-oestrone, 16β-OH-oesrone, 6α-OH-oestrone, 2-OH-17β-oestradiol, 6α-OH-17β-oestradiol, 16β-OH-7α-oestradiol, 17β-oestradiol, 2-methoxy-17β-oestradiol, 7α-OH-17β-oestradiol, 16α-OH-17β-oestradiol, 17α-ethenyl-17β-oestradiol, 4-OH-17β-oestradiol, 16α- OH-17α-oestradiol, 17α-oestradiol, 4-OH-oestriol, 2-OH-oestriol, 6α-OH-oestriol, 2-methoxy-oestriol, 7α-OH-oestriol, 6α-OH-dehydroepiandrosterone, 16α-OH-dehydroepiandrosterone, 7α-OH-dehydroepiandrosterone, and 16β-OH-dehydroepiandrosterone, or a pharmaceutically acceptable salt thereof.

3. The method of claim **1** or **2** wherein the steriod nucleus has the rings system ABCD of oestrone.

4. The method of claim **1** or **2** wherein the steroid nucleus has the rings system ABCD of 17β-oestradiol.

5. The method of claim **1** or **2** wherein the steroid nucleus has the rings system ABCD of 17α-ethyl-17β-oestradiol.

6. The method of claim **1** or **2** wherein the steroid nucleus has the rings system ABCD of 17α-oestradiol.

7. The method of claim **1** or **2** wherein the steroid nucleus has the rings ABCD of oestriol.

8. The method of claim **1** or **2** wherein R_1 and R_2 and H.

9. The method of claim **3** wherein R_1 and R_2 are H.

10. The method of claim **4** wherein R_1 and R_2 are H.

11. The method of claim **5** wherein R_1 and R_2 are H.

12. The method of claim **6** wherein R_1 and R_2 are H.

13. The method of claim **7** wherein R_1 and R_2 are H.

14. The method of claim **2** wherein the compound is oestrone-3-sulphmate (EMATE).

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,476,011 B1
DATED : October 2, 2001
INVENTOR(S) : Reed et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 51,
Line 62, please replace "4-n-propyl EMATA" with -- 4-n-propyl EMATE --.

Column 52,
Line 22, please replace "2,4-di-allyl EMATA" with -- 2,4-di-allyl EMATE --.
Line 23, please replace "2-methoxy EMATA" with -- 2-methoxy EMATE --.
Line 57, please replace "R_2 is II" with -- R_2 is H --.

Column 54,
Line 9, please replace "R2 and H" with -- R2 is H --.

Signed and Sealed this

Twelfth Day of August, 2003

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

EXHIBIT 2 TO:
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WITHDRAWAL OF OCTOBER 3, 2007 PETITION TO WITHDRAW FINALITY,
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INTERVIEW SUMMARY
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REQUEST FOR ANY NECESSARY EXTENSION OF TIME

Selective estrogen receptor modulation: Concept and consequences in cancer

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Extended exposure to the selective estrogen receptor modulators (SERMs) such as raloxifene to prevent osteoporosis and tamoxifen or the aromatase inhibitors to treat or prevent breast cancer are established therapeutic strategies. However, there are now clearly defined consequences of exhaustive antihormonal therapy in breast cancer. Ultimately, drug resistance to SERMs and aromatase inhibitors enhances cancer cell survival but a paradoxical supersensitivity to estrogen action develops that causes cancer cell apoptosis. The future exploitation of these novel data will allow selective killing of cancer with fewer side effects for patients.

Introduction

Estrogen mediates a broad spectrum of physiologic functions ranging from regulation of the menstrual cycle and reproduction to the modulation of bone density and cholesterol transport. The case for estrogen supplementation following menopause was based on the clinical observations that elderly women without circulating sex steroids had a higher incidence of osteoporotic fractures, coronary heart disease (CHD) and, most importantly for quality of life, hot flashes and night sweats. Conjugated equine estrogen alone was supplemented with medroxyprogesterone acetate to reduce the risk of endometrial cancer in postmenopausal women, and the combination is referred to as hormone replacement therapy (HRT). A regimen of HRT is effective in reducing osteoporotic fractures and is indispensable in treating severe menopausal symptoms (WGWHII, 2002). However, recent prospective clinical trials demonstrate that long-term HRT, i.e., 5 years or more, provides no overall benefit for women's health (MWSC, 2003; WGWHII, 2002). Although there are reductions in the incidence of colon cancer, osteoporotic fractures, and menopausal symptoms, there are increases in breast cancer, Alzheimer's disease, strokes, and blood clots (Figure 1; Chlebowski et al., 2003; MWSC, 2003; Shumaker et al., 2003; WGWHII, 2002). These definitive clinical studies have highlighted the opportunities for innovation in the selective modulation of estrogen target tissues (Figure 1).

Estrogen action at target sites around the body is mediated through related but distinct estrogen receptors (ERs) designated ERα and β (Enmark and Gustafsson, 1999). Estrogens bind to the ligand binding domain of the ER to induce a conformational change in protein structure that permits the subsequent dimerization and interaction with coactivator molecules (Figure 2; McDonnell and Norris, 2002; McKenna et al., 1999). The sequential activation of genes occurs through multiple mechanisms either directly at estrogen response elements in the promoter region of estrogen-responsive genes or through a tethering protein-protein interaction with c/os/jun B (AP-1) sites or Sp1 sites (Figure 2). These cellular signal transduction pathways can potentially be exploited to amplify tissue response selectivity. Alternatively, survival pathways in cancer could evolve to alter the entire responsiveness to ER signaling.

Traditionally, the science of pharmacology plays a critical role in drug discovery by using a receptor target to identify

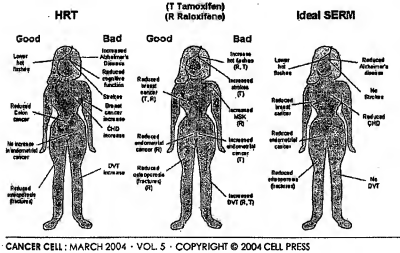

Figure 1. Progress toward an ideal SERM

The overall good or bad aspects of administering hormone replacement therapy to postmenopausal women compared with the observed site-specific actions of the selective estrogen receptor modulators tamoxifen and raloxifene. The known beneficial or negative actions of selective estrogen receptor modulators (SERMs) have opened the door for drug discovery to create the ideal SERM or targeted SERMs to either improve quality of life or prevent diseases associated with aging in women.

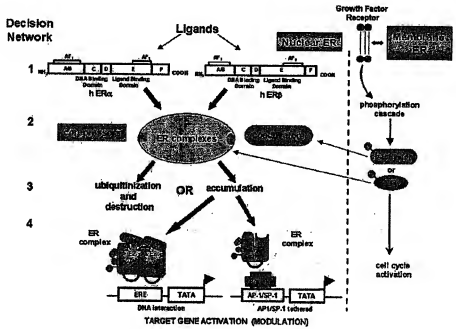

Figure 2. Complexity of SERM signal transduction

The decision network for estrogen or SERM action binding to nuclear estrogen receptor (ER) α or β receptor or membrane ER (decision 1). Receptor-specific or mixed specificity ligands bind to the ligand binding domain (E region) of the ERs to cause a ligand-specific perturbation in the receptor complex that creates opportunities for the complex to bind either coactivators or corepressors on the external surface (decision 2). The interactive proteins shunt the ER complex into transcriptionally active or inactive states. Although the expanding family of coregulators are being defined, this does not exclude the possibility of other interactive proteins could alter gene transcription through phosphorylation activation. This could be initiated rapidly either by membrane ER or constitutively through cell surface growth factor receptors. The next decision point (3) is where the complex or coregulators are ubiquitated and destroyed by the proteasome or accumulate to become promiscuous estrogen-like complexes. Again, phosphorylation may play an important role in the activity of the ER complex. The decision (4) to interact with the machinery involved with gene transcription can shunt the signaling pathway from positive or negative regulation based upon the ER concerned, the ligand, or whether there is a direct interaction with an estrogen response element (ERE) or a tethered interaction to proteins at AP-1 or SP-1 sites. Overall, the decision network creates a complex regulatory system of target tissues or in cancer where a growth advantage can be exploited in response to antiestrogen therapies.

select molecules for testing in the clinic. However, the recognition of the target tissues concept of selective estrogen receptor modulation by compounds originally referred to as nonsteroidal antiestrogens (Jordan, 1984) was noted first in laboratory animals and then successfully translated to the clinic (Jordan, 2001).

The clinical application of the SERM concept

The recognition of the SERM concept is an example of translational research that changed medical practice. Although the targeting of the ER with the nonsteroidal antiestrogen tamoxifen has increased selective survivorship in breast cancer (Jensen and Jordan, 2003), the strategic application of long-term antihormonal treatments (Jordan and Allen, 1980) has created an important increase in disease-free and overall survival (EBCTCG, 1998; Goss et al., 2003). However, tamoxifen is not a complete or pure antiestrogen, and the drug exhibits partial estrogen-like actions that could produce a suboptimal blockade of estrogen-stimulated breast tumor growth. Currently, aromatase inhibitors to produce an estrogen-free environment are demonstrating superiority to tamoxifen in controlling the growth of ER-positive breast cancer (ATAC Trialists' Group, 2002). Most importantly, the use of aromatase inhibitors for the treatment of breast cancer avoids some of the estrogen-like side effects observed in patients treated with tamoxifen. Tamoxifen is a partial estrogen agonists in the rodent uterus. Laboratory studies subsequently demonstrated that tamoxifen had the potential to stimulate growth of endometrial cancer but inhibit the growth of breast cancer (Gottardis et al., 1988). These data translated to a low but significant increase in the incidence of endometrial cancer in postmenopausal women treated with tamoxifen (Fisher et al., 1994; Fornander et al., 1989). However, the incidence of endometrial cancer is reduced during treatment with an aromatase inhibitor (ATAC Trialists' Group, 2002).

Clearly, the fact that tamoxifen increases the incidence of endometrial cancer is a significant concern for the application of tamoxifen as a chemopreventive for breast cancer in high-risk women. Nevertheless, the possibility that an antiestrogen could increase the risk for osteoporosis in well women was initially of greater concern for women's health in the 1980s. Tamoxifen maintains bone density in ovariectomized rats (Jordan et al., 1987; Turner et al., 1987), and this result translated to maintain-

ing bone density in postmenopausal patients (Love et al., 1992) with a nonsignificant reduction in fractures in a chemoprevention trial (Fisher et al., 1998). Thus, women with an increased risk for breast cancer treated with tamoxifen can anticipate a 50% reduction in the incidence of breast cancer (antiestrogenic) but a reduction of osteoporotic fractures (estrogenic) and an increase in the side effects of blood clots and endometrial polyps and cancer (estrogenic) (Figure 1; Fisher et al., 1998). This spectrum of SERM action creates a requirement for an intervention focused only on very high-risk woman and a requirement for new SERM discovery programs.

However, there is difficulty in identifying target populations in breast cancer. Clearly, a broader strategy was required to enhance the potential of SERMs in women's health to prevent breast cancer. The approach that was taken was to exploit the potential of SERMs to reduce osteoporotic fractures but with the beneficial side effect of reducing the incidence of breast cancer (Lerner and Jordan, 1990). The result is raloxifene, originally a discardad breast cancer drug named keoxifena. Raloxifene (keoxifane) maintains bone density in ovariectomized rats (Jordan et al., 1987) and prevents carcinogen-induced rat mammary carcinogenesis (Gottardis and Jordan, 1987). These data subsequently translated to the clinic where raloxifene is effective at reducing osteoporotic fractures in women at risk (Ettinger et al., 1999) with a reduction by 70% in the incidence of breast cancer (Cummings et al., 1999). Raloxifene is currently available for the prevention of osteoporosis but with breast and endometrial safety. Raloxifena is also being evaluated for the ability to reduce the incidenca of coronary heart disease (Mosca et al., 2001).

There is considerable interest in developing new SERMs as multifunctional agents in women's health (Jordan, 2003a, 2003b). However, the approach for the future will be based on the molecular modulation of emerging mechanisms rather than what happened in the past with the reinvention of nonsteroidal antiestrogens as receptor-targeted therapeutics from their original application as modulators of fertility (Jordan, 2003c).

Mechanisms of SERM action

The interpretation of a novel SERM at a target site involves a complex series of decision points that could shunt the receptor complex in one diraction or another (Figura 2). The challenge is first to document fully the machinery availeble et target sites and then to understand the subcelluler network of outcome opportunities. At present our basic understanding of the process is fregmentery, but current knowledga provides a reasonable basis for avaluating future targeted therapeutics (Figure 2).

The target site distribution of ERα and ERβ and differential ligand specificity and pharmacology (Enmerk and Gustafsson, 1999) have created opportunitias to develop receptor-specific ligands based primerily on differences in receptor affinity (Meyers et al., 2001; Stauffer et al., 2000). It is possible to envision tha development of an ERα-specific antagonist to prevent breast cancer or an ERβ-specific agonist to enhance CNS functions or prevent colon cancer. However, the process of drug dawalopment based on raceptor screening may be confounded by the complexities of the subsequent signal transduction pathways (Figure 2).

Considerable progress has been made during the past 5 years in understending the molecular perturbations that occur in the ligand binding domain of ERα and β when complexed with a SERM (Brzozowski et al., 1997; Pika et al., 2001; Shiau et al., 1998). The essential structural determinant of the SERM molecule is a correctly positioned alkylaminoethoxyphenyl side chain that interacts with asp351 in ERα to modulate antiastrogenic action through corepressor binding to the extarnel surface of the SERM receptor complex (Brzozowski et al., 1997; Shiau et al., 1998). The interaction of the SERM side chain with asp351 allostarically modulates the estrogenic and antiestrogenic action of tamoxifen and raloxifene. The tamoxifen ERα complex is much more promiscuous and astrogen-like than the raloxifane ERα complex, but estrogen and entiestrogan actions can be modulated by mutating asp351 (Liu et al., 2002; MacGregor Schafer et al., 2000). The interpretation of moleculer studies could go some wey to explaining the enhanced estrogan-like actions of tamoxifen in the uterus compared with raloxifene (Figure 1; Cummings et al., 1999; Fisher et al., 1998). Nevertheless, recent experimented evidence suggests thet there is anothar dimension involved in the estrogen-like action of SERMS.

The relativa concentretion of members of tha coactivator family (SRC-1, -2, or -3) or corepressors may regulate the response of a tissue to ERα. One possibility to explain target site specificity for SERM action would be to hava sita-specific coactivator interactions. Shang and Brown (2002) demonstrated, in one uterine cell line, that elevated SRC-1 anhanced tha estrogen-like actions of 4-hydroxytamoxifen but not raloxifane. This effact was not noted in breast cancer cells.

Ultimately, the response of a tissue to a ligand-receptor complex will depend not only on the efficacy but also the concentration of receptor complexes available to interact with the gene regulatory machinery. This consideration draws into the equation the dimension of receptor complex destruction. The higher the level of low-efficacy complexes, the higher the probability of estrogen action. However, the efficacy and concentretion of the activatad ligand receptor complex is regulated not only by sensitivity to ubiquitization of ER (Wijayaretne and McDonnell, 2001) and subsaquent destruction; the amount of coactivator proteins (Lonerd et al., 2004) is also important to amplify or suppress the activation of a complex.

SERMs increasa the levels of SRC-1 and -3 and also enhence the transcriptional activity of nuclear receptors other than ER in SERM-treated cells (Lonard et al., 2004). These events create additional opportunities for understanding tha complexity of target site specificity with SERMs. Indeed, tamoxifan-induced increases in SRC-3 have previously been shown to occur through the indirect action of SERM-induced transforming growth factor β (Lauritsen et al., 2002). Howavar, the complex preparations for gene transcription or protain activation are not the finel decision the SERM or estrogen must make. There appeer to be numerous additionel pathways that can modulate the individual cells in a target tissua. The simplistic view that the ER complex activates ganes through interaction with an ERE in the promotar ragion has evolved dramatically over the past decede. It seems that tha promoter region can influance the shape of the ER complex, which in turn can alter the external shape of an ER complex and, as a result, coactivator or corepressor binding (Hall et al., 2002). Select genes could be sequentially regulated by the changing conformation of an ER complex being modulated by promoter interactions.

It is now recognized that tha SERM ER complex is extremely promiscuous and can also activata genes through AP-1 (Webb et al., 1995) and SP-1 (Khan et al., 2003) (Figure 2) pro-

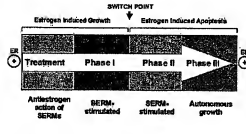

Figure 3. The evolution of drug resistance to SERMs

Acquired resistance occurs during long-term treatment with a SERM and is evidenced by SERM-stimulated breast tumor growth. Tumors also continue to exploit estrogen for growth when the SERM is stopped, as a dual signal transduction process develops. The aromatase inhibitors prevent tumor growth in SERM-resistant disease and fulvestrant that destroys the ER is also effective. This phase of drug resistance is referred to as Phase I resistance. Continued exposure to a SERM results in continued SERM-stimulated growth, but eventually autonomous growth (Phase II) occurs that is unresponsive to fulvestrant or aromatase inhibitors. The event that distinguishes Phase II from Phase II acquired resistance is a remarkable switching mechanism that now causes apoptosis, rather than growth, with physiologic levels of estrogen. These distinct phases of laboratory drug resistance (Lewis et al., 2004; Yao et al., 2000) have their clinical parallels and this new knowledge is being integrated into the treatment plan.

tein-protein interactions, and cell survival cascades may also be modulated by ER located in the cell membrane (Razandi et al., 1999). Most importantly, the bidirectional signaling between cell surface receptors (insulin-like growth factor and epidermal growth factor receptors) and ER will have profound effects on estrogen and SERM signaling opportunities (Levin, 2003). These membrane pathways can rapidly activate both ER and coactivators to enhance cell replication.

Overall, normal cells and tissues have the potential to be modulated by SERMs through a diverse and complex network of decision pathways. Understanding the potential targets will enhance the chances of novel designer SERMs to regulate or modulate numerous physiologic conditions. However, unlike the normal cell, the cancer cell adapts and evolves through selection in a changing drug environment. Understanding drug resistance to SERMs now creates new opportunities to exploit emerging discoveries in cancer cell regulatory pathways.

The evolution of drug resistance to SERMs

Twenty years ago, the development of drug resistance to antihormonal therapy in breast cancer was viewed as the insensitive ER-negative cells overgrowing ER-positive cells that were in growth arrest from antiestrogen treatment. Today, the conversation between the laboratory and the clinic has advanced therapeutics by recognizing various forms of drug resistance to tamoxifen. Current research is targeting resistance mechanisms to develop new therapeutic strategies. Resistance can be classified as either intrinsic resistance, where ER-positive breast cancer is initially refractory to antiestrogen treatment, or ER-positive disease that initially responds to antihormonal treatment but acquired resistance occurs subsequently. Acquired resistance can be caused by alterations in the ER signal transduction pathway converting the inhibitory SERM ERα complex to a growth stimulatory signal. Recent clinical studies (Osborne et al., 2003) indicate that tamoxifen is unlikely to be an effective therapy in ER-positive breast cancer patients who also have high levels of SRC-3 and HER2/neu. The cell surface signaling pathway can enhance phosphorylation of both the ER and SRC-3 (Font de Mora and Brown, 2000). These multiple opportunities to initially (intrinsic resistance) or eventually (acquired resistance) subvert the inhibitory actions of the tamoxifen ER complex creates a complex survival system for the cancer cell. This insight into the tumor options of either estrogen or tamoxifen-stimulated growth has resulted in improvements in therapeutics with either aromatase inhibitors that create a "no-estrogen" environment (ATAC Trialists' Group, 2002) or the pure antiestrogen fulvestrant (CI 182,780) that destroys the ER (Wiseyaratne and McDonnell, 2001). Both drug types are valuable for the treatment of tamoxifen-resistant breast cancer (Robertson et al., 2003).

However, current understanding of drug resistance to SERMs or estrogen deprivation is based on short-term (1–2 years) treatment periods. This treatment strategy was appropriate 25 years ago when the focus was on treating advanced disease, but today all trends are toward a decade of treatment in breast cancer (Goss et al., 2003) or indefinite treatment with raloxifene for the prevention of osteoporosis. Recently, the

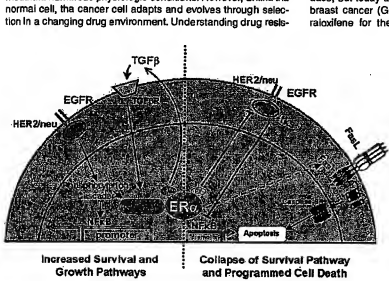

Figure 4. Life and death of Phase II SERM resistance

Putative mechanisms of estradiol (E2)-induced apoptosis that occurs after the switch point in Phase II and Phase III SERM resistance. Drug resistance to SERMs occurs when the ER survival signal transduction pathway is blocked. Surviving cancer cells create enhanced cell-surface signaling mechanisms (HER2/neu, EGFR) that initiate phosphorylation cascades that enhance the activity of the SERM-ER complex either directly or indirectly through transforming growth factor β (TGFβ) and inducing coactivators that are phosphorylated. Long-term SERM exposure creates sophisticated, yet vulnerable, survival pathways that can be collapsed rapidly by estradiol with a loss of HER2/neu signaling and loss of prosurvival NFκB. The events that herald apoptosis occur in parallel during estradiol treatment. The death receptor Fas is translated and a cascade of caspase activation condenses the chromatin and destroys the cell.

description of models of extended antihormonal therapy now provide new opportunities for reusing the ER as a novel therapeutic target in cancer (Figure 3).

The repeated transplantation of MCF-7 tamoxifen-resistant breast tumors into successive generations of tamoxifen-treated athymic mice or culture of MCF-7 cells under estrogen-free conditions with or without raloxifene results in the alteration of the signal transduction pathways for estrogen (Liu et al., 2003; Yao et al., 2000). Although astrogen is considered to be a survival hormone with the ability to initiate replication, drug resistance to estrogen deprivation occurs by developing cells with enhanced survival pathways that maintain the growth advantage for cancer cells. For example, cell surface signaling through HER2/neu is regulated by estrogen: without estrogen, HER2/neu mRNA is increased (Newman et al., 2000).

Exhaustive antiendocrine therapy causes the ultimate form of drug resistance, spontaneous growth (Figure 3). However, studies in the laboratory (Yao et al., 2000) and preliminary clinical studies (Lonning et al., 2001) demonstrate that estrogen, rather than acting as a growth stimulus, acts as an apoptotic agent through an ER-mediated mechenism in Phase II and Phase III resistant disease (Figure 3).

Clearly, there is potential to incorporate an "estrogen purge" into the long-term clinical treatment program. Laboratory studies already demonstrate that tumors that recur after estrogen-induced apoptosis are again sensitive to the antitumor actions of tamoxifen or estrogen withdrawal (aromatase inhibitor) (Yao et al., 2000). A strategy of cyclical antihormone treatment and estrogen purges may maintain patients with breast cancer for decades.

Molecular mechanisms of estrogen-induced apoptosis

Preliminary subcellular studies have identified the fas/fas ligand pathway as a putative mediator of estrogen-induced apoptosis in both long-term estrogen-deprived cells (a model of aromatase inhibition) (Song et al., 2001) and either tamoxifen- or raloxifene-resistant breast cancer cells (Liu et al., 2003; Osipo et al., 2003). The cancer cell survival pathways mediated by the HER2/neu cell surface signaling mechanisms collapse and so does the nuclear NFκB transcription mechanism. In parallel, estrogen induces the fas receptor (Liu et al., 2003; Osipo et al., 2003) that may herald apoptosis (Figure 4).

Overall, these studies provide an insight into the balance of cell survival and apoptosis that occurs through the ER. However, the unanticipated result that the pure antiestrogen fulvestrant blocks the estrogen-induced apoptotic pathway and enhances robust tumor growth by maintaining survival pathways (Osipo et al., 2003) illustrates the delicate balance between survival and cell death governed by the ER. A similar phenomenon occurs in the long-term estrogen-deprived cell line MCF-7:5C (Lewis et al., 2004). Estrogen induces rapid apoptosis in vitro and in vivo when autonomously growing cells are transplanted into athymic mice. However, the combined effect of the antiestrogen fulvestrant alone and the apoptotic effect of estrogen alone results in maximal growth of MCF-7:5C cells when both estrogen and fulvestrant are incubated together (unpublished data). It is also possible to provoke estrogen-independent growth in another breast cancer cell line T47D stably transfected with the cDNA for PKC α. Tumors grow spontaneously in athymic mice, but again estrogen rapidly causes tumor regressions through apoptosis (Chisamore et al., 2001).

Overall, it seems that a new general principle is emerging where the creation of an enhanced survival network in the cancer cell can be rapidly destroyed by the use of estrogen targeted to the ER. Discovery of the cellular survival mechanisms that subvert the central role of the ER in breast cancer may provide new advances in targeted therapies. Currently, the observation that half of the ER-positive breast cancers are responsive to antihormones could be viewed as an opportunity to restrict survival selectively with novel tyrosine kinase inhibitors and then activate the ER with either traditional or low-dose astrogen. The ER could also be used as the bait to discover a novel apoptotic target to exploit in future drug discovery.

Summary of SERM prospects

The successful therapeutic application of antihormonal strategies with tamoxifen and aromatase inhibitors has probably reached its zenith in the clinic, but study of drug resistance has now opened a new chapter in targeting cancer. There is currently a separation of objectives, with the aromatase inhibitors being used predominantly to treat breast cancer and the SERMs providing therapeutic opportunities as safer "hormone replacement" therapies to prevent osteoporosis and reduce breast and endometrial cancer (Figure 1). Nevertheless, extended or perhaps indefinite treatment regimes are now possible if late-phase antihormonally resistant disease can be destroyed with a short estrogen purge. Additionally, there are practical opportunities to broaden the value of the ER as a therapeutic target by devising logical treatment strategies for the patient with an ER-positive tumor that is refractory to antihormonal treatment. Although these new treatment options could potentially benefit patients, it is the potential of the ER to identify a novel apoptotic target that could dramatically advance selectivity in molecular therapeutics.

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EXHIBIT 3 TO:
AMENDMENT AFTER FINAL ACTION
&
WITHDRAWAL OF OCTOBER 3, 2007 PETITION TO WITHDRAW FINALITY,
TO WITHDRAW JULY 3, 2007 OFFICE ACTION, FOR INTERVIEW,
AND FOR CORRECT / PROPER OFFICE ACTIONS
&
INTERVIEW SUMMARY
&
REQUEST FOR ANY NECESSARY EXTENSION OF TIME

Hormonal approaches to the chemoprevention of endocrine-dependent tumors

A Manni

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Abstract

The estrogen dependency of human breast cancer has been successfully exploited in the treatment of early and advanced diseases and provides a unique opportunity for chemoprevention of this common malignancy. Preliminary results with the antiestrogens Tamoxifen and Raloxifene show an encouraging reduction in the incidence of breast cancer. Alternative approaches include the use of highly selective and non-toxic aromatase inhibitors and, in premenopausal women, the use of LHRH agonists in conjunction with the administration of small doses of estrogen and progesterone. The rationale for these chemopreventive strategies and their possible limitations are briefly discussed

Endocrine-Related Cancer (1999) **6** 483-485

The importance of ovarian hormones in the development of most, if not all, human breast cancers is widely appreciated. The increased risk of breast cancer conferred by early menarche and late menopause points to the importance of cumulative exposure to ovarian hormones as a determinant of mammary carcinogenesis. Among ovarian hormones, estradiol has clearly emerged as the predominant one involved in human breast cancer. In the author's opinion, the role of progesterone, while possibly important, is less clearly defined. Both proliferative and antiproliferative effects of progesterone have been reported in breast epithelial cells (Meyer 1977, Masters *et al.* 1977, Barrat *et al.* 1990, Chang *et al.* 1995). Furthermore, progesterone has a clear role in inducing alveolar differentiation which, at least in rodents, has been shown to have a protective effect on experimentally induced mammary carcinogenesis (Segaloff 1973). The role of estrogens, on the other hand, appears to be more straightforward. A recently published meta-analysis has shown a positive association between serum estradiol concentration and breast cancer risk in postmenopausal women (Thomas *et al.* 1997). Furthermore, local estrogen production in the breast tissue itself has received increasing attention as a major contributor to breast cancer development (Santner *et al.* 1997, Bulun *et al.* 1996). These observations indicate that estrogens contribute to mammary carcinogenesis both in an endocrine and paracrine fashion. There are at least two mechanisms by which estrogens could promote breast cancer formation (Santen *et al.* 1999). The prevailing theory is that estrogens increase the number of mutations as a result of their receptor-mediated, growth-promoting effect. An alternative, not mutually exclusive, possibility is that estrogens are metabolized to genotoxic products which cause direct DNA damage independently of the presence of the estrogen receptor.

The estrogen dependency of human breast cancer has been successfully exploited therapeutically in the treatment of both advanced and early disease. Therefore, it is not surprising that effective interference with estrogen action or biosynthesis is being actively pursued in the chemoprevention of breast cancer. Encouraging preliminary results have already started to emerge with the use of Tamoxifen in the NSABP-P1 trial involving 13 388 high-risk women, where a 45% reduction in the incidence of invasive breast cancer was observed in the treated compared with the placebo group (Fisher 1998). Similar results have been reported with the selective estrogen receptor modulator, Raloxifene, in the multiple outcomes of Raloxifen evaluation (MORE) trial involving 7704 postmenopausal women with osteoporosis (i.e. not at increased risk of breast cancer) (Cummings *et al.* 1998). These findings need to be interpreted with caution because of the short duration of follow-up. Furthermore, two smaller European studies, the Royal Marsden Hospital Chemoprevention Trial (Powles *et al.* 1998) and the Italian Tamoxifen Prevention Study (Veronesi *et al.* 1998), have failed to demonstrate any reduction in breast cancer incidence with Tamoxifen.

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Highly selective and non-toxic aromatase inhibitors are also being considered for breast cancer chemoprevention (Santen *et al.* 1999). They may offer a few theoretical advantages over antiestrogens within this context. In premenopausal women, they may selectively deplete local estrogen production in the breast tissue without affecting systemic estrogen levels, since the ovary is resistant to the action of aromatase inhibitors. If, indeed, local estrogen production is the major determinant of mammary carcinogenesis, aromatase inhibitors would offer protection from breast cancer while preserving the beneficial effects of circulating estrogens on the host. An additional theoretical advantage of aromatase inhibitors is their potential ability to counteract both receptor-mediated and direct genotoxic effects of estrogens, while only the former would be expected to be influenced by antiestrogen therapy. At present, however, the role of aromatase inhibitors in breast cancer chemoprevention remains theoretical, since no clinical data are yet available.

Dr Malcolm Pike has pioneered a different endocrine approach to the chemoprevention of hormone-dependent tumors. He and his co-workers propose to suppress ovarian function with GnRH analogue therapy and to add back low doses of estrogen and progesterone which would be insufficient to promote mammary and uterine carcinogenesis but would be high enough to provide beneficial effects such as cardiac protection and bone preservation (Spicer & Pike 1994). A significant potential advantage of this approach over those discussed above is that it would reduce the risk, not only of breast cancer, but also of ovarian and endometrial cancer. According to Dr Pike's estimate, this contraceptive regimen, applied for five years, would reduce breast cancer risk by 30%, ovarian cancer risk by 40%, and endometrial cancer risk by 20%. In a pilot study involving 21 young women (14 assigned to the contraceptive regimen and 7 to no treatment), Dr Pike reported a significant reduction in mammographic densities at 1 year in hormonally treated women compared with the control group (Spicer *et al.* 1994). It is hoped that a reduction in mammographic densities will translate into reduced breast cancer risk, although there is no direct evidence to support this assumption. Reduction in mammographic densities will also be the end point of a multi-center, 12-month study including a small group of high-risk premenopausal women (mostly with BRCA-1 mutations) who will be placed on a similar contraceptive regimen with additional administration of low doses of testosterone (Weitzel 1999).

Every attempt at endocrine chemoprevention of breast cancer (and other endocrine-related tumors) faces the same challenge, i.e. eliminating the adverse hormonal effects on carcinogenesis while preserving their multiple beneficial actions, such as those on bones, heart, sexuality and possibly brain. The development and introduction of SERMS represent a logical approach to address this issue which is based upon improved understanding of the molecular mechanisms of estrogen action. It should be recognized, however, that both Tamoxifen and Raloxifene, the only two SERMS currently available in clinical practice, are still in their infancy as chemopreventive agents. First of all, the still relatively short duration of follow-up of both the NSABP-P1 and MORE trials does not allow us to categorically distinguish between true chemoprevention and a suppressive effect on already established tumors. Secondly, Tamoxifen use has been found to be associated with increased risks of endometrial cancer and thromboembolic events. These side effects need to be taken into serious consideration since normal women, not patients with breast cancer, are being considered for long-term treatment. The approach proposed by Dr Pike has a sound biological rationale, but still remains theoretical at this point. Data beyond reduction in mammographic densities will need to be generated to prove the efficacy of this regimen. Furthermore, the safety of long-term administration of GnRH analogue therapy in young women needs to be demonstrated. In addition, this protocol is quite complex and its practical applicability on a large scale could be questioned.

Finally, all protocols still face many unresolved issues such as definition of the optimal demographic characteristics of the target populations (e.g. age, risk factor profiles), as well as the identification of optimal duration of treatment. In sum, chemoprevention of hormone-dependent cancers is truly a multi-disciplinary effort which will require improved understanding of the molecular biology of hormone action on neoplastic and normal tissues and a more clear definition of the genetic changes leading to carcinogenesis, as well as a better appreciation of their interaction with epigenetic events.

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TO WITHDRAW JULY 3, 2007 OFFICE ACTION, FOR INTERVIEW,
AND FOR CORRECT / PROPER OFFICE ACTIONS
&
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Description

[0001] Evidence suggests that oestrogens are the major mitogens involved in promoting the growth of tumours in endocrine-dependent tissues, such as the breast and endometrium. Although plasma oestrogen concentrations are similar in women with or without breast cancer, breast tumour oestrone and oestradiol levels are significantly higher than in normal breast tissue or blood. *In situ* synthesis of oestrogen is thought to make an important contribution to the high levels of oestrogens in tumours and therefore specific inhibitors of oestrogen biosynthesis are of potential value for the treatment of endocrine-dependent tumours.

[0002] Over the past two decades, there has been considerable interest in the development of inhibitors of the aromatase pathway which converts the androgen precursor androstenedione to oestrone. However, there is now evidence that the oestrone sulphatase (E1-STS) pathway, i.e. the hydrolysis of oestrone sulphate to oestrone (E1S to E1), as opposed to the aromatase pathway, is the major source of oestrogen in breast tumours[1,2]. This theory is supported by a modest reduction of plasma oestrogen concentration in postmenopausal women with breast cancer treated by aromatase inhibitors, such as aminoglutethimide and 4-hydroxyandrostenedione[3,4] and also by the fact that plasma E1S concentration in these aromatase inhibitor-treated patients remains relatively high. The long half-life of E1S in blood (10-12 h) compared with the unconjugated oestrogens (20 min)[5] and high levels of steroid sulphatase activity in liver and, normal and malignant breast tissues, also lend support to this theory[6].

[0003] PCT/GB92/01587 teaches novel steroid sulphatase inhibitors and pharmaceutical compositions containing them for use in the treatment of oestrone dependent tumours, especially breast cancer. These steroid sulphatase inhibitors are sulphamate esters, such as N,N-dimethyl oestrone-3-sulphamate and, preferably, oestrone-3-sulphamate (otherwise known as "EMATE").

[0004] Some of the compounds disclosed in PCT/GB92/01587 are shown in Figure 1.

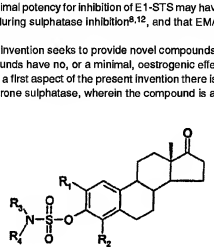
[0005] It is known that EMATE is a potent E1-STS inhibitor as it displays more than 99% inhibition of E1-STS activity in intact MCF-7 cells at 0.1 *m*M. EMATE also inhibits the E1-STS enzyme in a time- and concentration-dependent manner, indicating that it acts as an active site-directed inactivator[7,8]. Although EMATE was originally designed for the inhibition of E1-STS, it also inhibits dehydroepiandrosterone sulphatase (DHA-STS), which is an enzyme that is believed to have a pivotal role in regulating the biosynthesis of the oestrogenic steroid androstenediol[8,9]. Also, there is now evidence to suggest that androstenediol may be of even greater importance as a promoter of breast tumour growth[10]. EMATE is also active *in vivo* as almost complete inhibition of rat liver E1-STS (99%) and DHA-STS (99%) activities resulted when it is administered either orally or subcutaneously[11]. In addition, EMATE has been shown to have a memory enhancing effect in rats[14]. Studies in mice have suggested an association between DHA-STS activity and the regulation of part of the immune response. It is thought that this may also occur in humans[15,16]. The bridging *O*-atom of the sulphamate moiety in EMATE is important for inhibitory activity. Thus, when the 3-*O*-atom is replaced by other heteroatoms (Figure 1) as in oestrone-3-*N*-sulphamate (4) and oestrone-3-*S*-sulphamate (5), these analogues are weaker non-time-dependent inactivators[12].

[0006] Although optimal potency for inhibition of E1-STS may have been attained in EMATE, it is possible that oestrone may be released during sulphatase inhibition[8,12], and that EMATE and its oestradiol congener may possess oestrogenic activity[13].

[0007] The present invention seeks to provide novel compounds suitable for the inhibition of E1-STS but preferably wherein those compounds have no, or a minimal, oestrogenic effect.

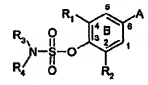
[0008] According to a first aspect of the present invention there is provided a sulphamate compound suitable for use as an inhibitor of oestrone sulphatase, wherein the compound is a sulphamate compound having Formula V;

Formula V



wherein each of R_1 and R_2 is independently selected from H, alkyl, cycloalkyl, alkoxy, alkenyl, aryl, substituted alkyl, substituted cycloalkyl, substituted alkenyl, substituted aryl, a nitrogen containing group, a S containing group, or a carboxy containing group; R_1 and R_2 may be the same or different but not both being H; and each of R_3 and R_4 is independently selected from H, alkyl, cycloalkyl, alkenyl and aryl, wherein at least one of R_3 and R_4 is H.

[0009] According to a second aspect of the present invention there is provided a sulphamate compound suitable for use as an inhibitor of oestrone sulphatase, wherein the compound is a sulphamate compound having Formula II;



Formula II

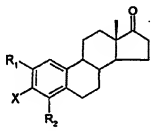
wherein R_1 is selected from alkyl, cycloalkyl, alkoxy, alkenyl, aryl, substituted alkyl, substituted cycloalkyl, substituted alkenyl, substituted aryl, a nitrogen containing group, a S containing group, or a carboxy containing group; R_2 is selected from H, alkyl, cycloalkyl, alkoxy, alkenyl, aryl, substituted alkyl, substituted cycloalkyl, substituted alkenyl, substituted aryl, a nitrogen containing group, a S containing group, or a carboxy containing group; R_1 and R_2 may be the same or different; each of R_3 and R_4 is independently selected from H, alkyl, cycloalkyl, alkenyl and aryl, wherein at least one of R_3 and R_4 is H; group A and ring B together are capable of mimicking the A and B rings of oestrone; and group A is additionally attached to the carbon atom at position 1 of the ring B.

[0010] According to a third aspect of the present invention there is provided use of a compound in the manufacture of a medicament to inhibit steroid sulphatase activity, wherein the compound is a sulphamate compound having Formula II;

Formula II

wherein X is a sulphamate group; R_1 is selected from alkyl, cycloalkyl, alkoxy, alkenyl, aryl, substituted alkyl, substituted cycloalkyl, substituted alkenyl, substituted aryl, a nitrogen containing group, a S containing group, or a carboxy containing group; and R_2 is selected from H, alkyl, cycloalkyl, alkoxy, alkenyl, aryl, substituted alkyl, substituted cycloalkyl, substituted alkenyl, substituted aryl, a nitrogen containing group, a S containing group, or a carboxy containing group; R_1 and R_2 may be the same or different; wherein group A and ring B together are capable of mimicking the A and B rings of oestrone; and wherein group A is additionally attached to the carbon atom at position 1 of the ring B.

[0011] According to a fourth aspect of the present invention there is provided a 4. Use of a compound in the manufacture of a medicament to inhibit steroid sulphatase activity, wherein the compound is a sulphamate compound having Formula V;



Formula V

wherein X is a sulphamate group; each of R_1 and R_2 is independently selected from H, alkyl, cycloalkyl, alkoxy, alkenyl, aryl, substituted alkyl, substituted cycloalkyl, substituted alkenyl, substituted aryl, a nitrogen containing group, a S containing group, or a carboxy containing group; and R_1 and R_2 may be the same or different but not both being H.

[0012] The term "mimic" as used herein means having a similar or different structure but having a similar functional effect. In otherwords, group A and ring B together of the compounds of the present invention are bio-isosteres of the A and B rings of oestrone.

[0013] A key advantage of the present invention is that the sulphamate compounds of the present invention can act

as E1-STS inhibitors.

[0014] Another advantage of the compounds of the present invention is that they may be potent *in vivo* and that they may have less oestrogenic activity than the known compounds and can therefore be deemed to be a "non-oestrogenic compound". The term "non-oestrogenic compound" as used herein means a compound exhibiting no or substantially no oestrogenic activity.

[0015] The present invention therefore provides sulphamate compounds which may have a reduced oestrogenic activity.

[0016] Another advantage is that the compounds may not be capable of being metabolised to compounds which display or induce hormonal activity.

[0017] The compounds of the present invention are also advantageous in that they may be orally active.

[0018] The compounds of the present invention are further advantageous in that they may have an irreversible effect.

[0019] In a preferred embodiment, the sulphamate compounds of the present invention are useful for the treatment of breast cancer.

[0020] In addition, the sulphamate compounds of the present invention are useful for the treatment of non-malignant conditions, such as the prevention of auto-immune diseases, particularly when pharmaceuticals may need to be administered from an early age.

[0021] The sulphamate compounds of the present invention are also believed to have therapeutic uses other than for the treatment of endocrine-dependent cancers, such as the treatment of autoimmune diseases.

[0022] Preferably, group A and ring B are a steroid ring structure or a substituted derivative thereof.

[0023] The term "sulphamate" as used herein includes an ester of sulphamic acid, or an ester of an N-substituted derivative of sulphamic acid, or a salt thereof.

[0024] Preferably, the sulphamate group has the Formula III.

[0025] R_3 and R_4 are independently selected from H or alkyl, cycloalkyl, alkenyl and aryl, or together represent alkylene, wherein the or each alkyl or cycloalkyl or alkenyl or optionally contain one or more hetero atoms or groups.

[0026] When substituted, the N-substituted compounds of this invention may contain one or two N-alkyl, N-alkenyl, N-cycloalkyl or N-aryl substituents, preferably containing or each containing a maximum of 10 carbon atoms. When R_3 and/or R_4 is alkyl, the preferred values are those where R_3 and R_4 are each independently selected from lower alkyl groups containing from 1 to 5 carbon atoms, that is to say methyl, ethyl, propyl etc. Preferably R_3 and R_4 are both methyl. When R_3 and/or R_4 is aryl, typical values are phenyl and tolyl (-$PhCH_3$; *o*-, *m*- or *p*-). Where R_3 and R_4 represent cycloalkyl, typical values are cyclopropyl, cyclopentyl, cyclohexyl etc. When joined together R_3 and R_4 typically represent an alkylene group providing a chain of 4 to 6 carbon atoms, optionally interrupted by one or more hetero atoms or groups, e.g. -O- or -NH- to provide a 5-, 6- or 7- membered heterocycle, e.g. morpholino, pyrrolidino or piperidino.

[0027] Within the values alkyl, cycloalkyl, alkenyl and aryl we include substituted groups containing as substituents therein one or more groups which do not interfere with the sulphatase inhibitory activity of the compound in question. Exemplary non-interfering substituents include hydroxy, amino, halo, alkoxy, alkyl and aryl.

[0028] In some preferred embodiments, at least one of R_3 and R_4 is H.

[0029] In some further preferred embodiments, each of R_3 and R_4 is H.

[0030] Preferably, each of R_1 and R_2 is independently selected from H, alkyl, cycloalkyl, alkenyl, aryl, substituted alkyl, substituted cycloalkyl, substituted alkenyl, substituted aryl, any other suitable hydrocarbyl group, a nitrogen containing group, a S containing group, a carboxy containing group.

[0031] Likewise, here, the term "hydrocarbyl group" means a group comprising at least C and H and may optionally comprise one or more other suitable substituents. Examples of such substituents may include halo-, alkoxy-, nitro-, an alkyl group, a cyclic group etc. In addition to the possibility of the substituents being a cyclic group, a combination of substituents may form a cyclic group. If the hydrocarbyl group comprises more than one C then those carbons need not necessarily be linked to each other. For example, at least two of the carbons may be linked *via* a suitable element or group. Thus, the hydrocarbyl group may contain hetero atoms. Suitable hetero atoms will be apparent to those skilled in the art and include, for instance, sulphur, nitrogen and oxygen. A non-limiting example of a hydrocarbyl group is an acyl group.

[0032] Preferably, each of R_1 and R_2 is independently selected from H, C_{1-6} alkyl, C_{1-6} cycloalkyl, C_{1-6} alkenyl, substituted C_{1-6} alkyl, substituted C_{1-6} cycloalkyl, substituted C_{1-6} alkenyl, substituted aryl, a nitrogen containing group, a S containing group, or a carboxy group having from 1-6 carbon atoms.

[0033] Likewise, here within the values alkyl, cycloalkyl, alkenyl and aryl we include substituted groups containing as substituents therein one or more groups which do not interfere with the sulphatase inhibitory activity of the compound in question. Exemplary non-interfering substituents include hydroxy, amino, halo, alkoxy, alkyl and aryl.

[0034] Preferably, each of R_1 and R_2 is independently selected from H, C_{1-6} alkyl, C_{1-6} alkenyl, a nitrogen containing group, or a carboxy group having from 1-6 carbon atoms.

[0035] Preferably, each of R_1 and R_2 is independently selected from H, C_{1-6} alkyl, C_{1-6} alkenyl, NO_2, or a carboxy containing group having from 1-6 carbon atoms.

[0036] Preferably, each of R_1 and R_2 is independently selected from H, C_3 alkyl, C_3 alkenyl, NO_2, or H_3CO.

[0037] Preferably, the compound is any one of the Formulae V - IX.

[0038] Preferably, for some applications, the compound is further characterised by the feature that if the sulphamate group were to be substituted by a sulphate group to form a sulphate derivative, then the sulphate derivative would be hydrolysable by an enzyme having steroid sulphatase (E.C. 3.1.6.2) activity - i.e. when incubated with steroid sulphatase EC 3.1.6.2 at pH 7.4 and 37°C.

[0039] In one preferred embodiment, if the sulphamate group of the compound were to be replaced with a sulphate group to form a sulphate compound then that sulphate compound would be hydrolysable by an enzyme having steroid sulphatase (E.C. 3.1.6.2) activity and would yield a K_m value of less than 50mmolar when incubated with steroid sulphatase EC 3.1.6.2 at pH 7.4 and 37°C.

[0040] In another preferred embodiment, if the sulphamate group of the compound were to be replaced with a sulphate group to form a sulphate compound then that sulphate compound would be hydrolysable by an enzyme having steroid sulphatase (E.C. 3.1.6.2) activity and would yield a K_m value of less than 50µmolar when incubated with steroid sulphatase EC 3.1.6.2 at pH 7.4 and 37°C.

[0041] In a highly preferred embodiment, the compound of the present invention is not hydrolysable by an enzyme having steroid sulphatase (E.C. 3.1.6.2) activity.

[0042] Thus, the present invention provides novel sulphamate compounds.

[0043] Preferably the group A and the ring B together - hereinafter referred to as "group A/ring B combination" - will contain, inclusive of all substituents, a maximum of about 50 carbon atoms, more usually no more than about 30 to 40 carbon atoms.

[0044] A preferred group A/ring B combination has a steroidal ring structure, that is to say a cyclopentanophenanthrene skeleton. Preferably, the sulphamyl or substituted sulphamyl group is attached to that skeleton in the 3-position.

[0045] Thus, according to a preferred embodiment, the group A/ring B combination is a substituted or unsubstituted, saturated or unsaturated steroid nucleus.

[0046] A suitable steroid nucleus is a substituted (i.e. substituted in at least the 2 and/or 4 position and optionally elsewhere in the steroid nucleus) derivative of any one of: oestrone, 2-OH-oestrone, 2-methoxy-oestrone, 4-OH-oestrone, 6a-OH-oestrone, 7a-OH-oestrone, 16a-OH-oestrone, 16b-OH-oestrone, oestradiol, 2-OH-17b-oestradiol, 2-methoxy-17b-oestradiol, 4-OH-17b-oestradiol, 6a-OH-17b-oestradiol, 7a-OH-17b-oestradiol, 16a-OH-17a-oestradiol, 16b-OH-17a-oestradiol, 16b-OH-17b-oestradiol, 17a-oestradiol, 17b-oestradiol, 17a-ethinyl-17b-oestradiol, oestriol, 2-OH-oestriol, 2-methoxy-oestriol, 4-OH-oestriol, 6a-OH-oestriol, 7a-OH-oestriol, dehydroepiandrosterone, 6a-OH-dehydroepiandrosterone, 7a-OH-dehydroepiandrosterone, 16a-OH-dehydroepiandrosterone, 16b-OH-dehydroepiandrosterone.

[0047] In general terms the group A/ring B combination may contain a variety of non-interfering substituents. In particular, the group A/ring B combination may contain one or more hydroxy, alkyl especially lower (C_1-C_6) alkyl, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl and other pentyl isomers, and n-hexyl and other hexyl isomers, alkoxy especially lower (C_1-C_6) alkoxy, e.g. methoxy, ethoxy, propoxy etc., alkenyl, e.g. ethenyl, or halogen, e.g. fluoro substituents.

[0048] The group A/ring B combination may even be a non-steroidal ring system.

[0049] A suitable non-steroidal ring system is a substituted (i.e. substituted in at least the 2 and/or 4 position and optionally elsewhere in the ring system) derivative of any one of: diethylstilboestrol, stilboestrol.

[0050] When substituted, the N-substituted compounds of this invention may contain one or two N-alkyl, N-alkenyl, N-cycloalkyl or N-aryl substituents, preferably containing or each containing a maximum of 10 carbon atoms.

[0051] When R_1 and/or R_2 and/or R_3 and/or R_4 is alkyl, the preferred values are those where each of R_1 and R_2 and R_3 and R_4 is independently selected from lower alkyl groups containing from 1 to 6 carbon atoms, that is to say methyl, ethyl or propyl.

[0052] When R_1 and/or R_2 and/or R_3 and/or R_4 is aryl, typical groups are phenyl and tolyl (-$PhCH_3$; *o*-, *m*- or *p*-).

[0053] Where R_1 and/or R_2 and/or R_3 and/or R_4 represent cycloalkyl, typical values are cyclopropyl, cyclopentyl or cyclohexyl.

[0054] When joined together R_3 and R_4 typically represent an alkylene group providing a chain of 4 to 8 carbon atoms, optionally interrupted by one or more hetero atoms or groups, e.g. -O- or -NH- to provide a 5-, 6- or 7- membered heterocycle, e.g. morpholino, pyrrolidino or piperidino.

[0055] Within the values alkyl, cycloalkyl, alkenyl and aryl we include substituted groups containing as substituents therein one or more groups which do not interfere with the sulphatase inhibitory activity of the compound in question. Examples of non-interfering substituents include hydroxy, amino, halo, alkoxy, alkyl and aryl.

[0056] Any replacement for H on the ring system may be any one of the substituents described above in relation to R_1 and R_2.

[0057] According to a further aspect of the present invention there is provided a sulphamate compound according to the present invention for use as a pharmaceutical.

[0058] According to a further aspect of the present invention there is provided a sulphamate compound according to the present invention for inhibiting oestrone sulphatase.

[0059] According to a further aspect of the present invention there is provided a pharmaceutical composition comprising a sulphamate compound according to the present invention; and a pharmaceutically acceptable carrier, excipient, adjuvant or diluent.

[0060] According to a further aspect of the present invention there is provided the use of a sulphamate compound according to the present invention in the manufacture of a pharmaceutical for inhibiting oestrone sulphatase.

[0061] The sulphamate compounds of the present invention may be prepared by reacting an appropriate alcohol with a sulfamoyl chloride, $R_3R_4NSO_2Cl$.

[0062] Preferred conditions for carrying out the reaction are as follows.

[0063] Sodium hydride and a sulfamoyl chloride are added to a stirred solution of the alcohol in anhydrous dimethyl formamide at 0°C. Subsequently, the reaction is allowed to warm to room temperature whereupon stirring is continued for a further 24 hours. The reaction mixture is poured onto a cold saturated solution of sodium bicarbonate and the resulting aqueous phase is extracted with dichloromethane. The combined organic extracts are dried over anhydrous $MgSO_4$. Filtration followed by solvent evaporation *in vacuo* and co-evaporated with toluene affords a crude residue which is further purified by flash chromatography.

[0064] Preferably, the alcohol is derivatised, as appropriate, prior to reaction with the sulfamoyl chloride. Where necessary, functional groups in the alcohol may be protected in known manner and the protecting group or groups removed at the end of the reaction.

[0065] For pharmaceutical administration, the steroid sulphatase inhibitors of this invention can be formulated in any suitable manner utilising conventional pharmaceutical formulating techniques and pharmaceutical carriers, adjuvants, excipients, diluents etc. and usually for parenteral administration. Approximate effective dose rates are in the range 100 to 800 mg/day depending on the individual activities of the compounds in question and for a patient of average (70Kg) bodyweight. More usual dosage rates for the preferred and more active compounds will be in the range 200 to 800 mg/day, more preferably, 200 to 500 mg/day, most preferably from 200 to 250 mg/day. They may be given in single dose regimes, split dose regimes and/or in multiple dose regimes lasting over several days. For oral administration they may be formulated in tablets, capsules, solution or suspension containing from 100 to 500 mg of compound per unit dose. Alternatively and preferably the compounds will be formulated for parenteral administration in a suitable parenterally administrable carrier and providing single daily dosage rates in the range 200 to 800 mg, preferably 200 to 500, more preferably 200 to 250 mg. Such effective daily doses will, however, vary depending on inherent activity of the active ingredient and on the bodyweight of the patient, such variations being within the skill and judgement of the physician.

[0066] For particular applications, it is envisaged that the steroid sulphatase inhibitors of this invention may be used in combination therapies, either with another sulphatase inhibitor, or, for example, in combination with an aromatase inhibitor, such as for example, 4-hydroxyandrostenedione (4-OHA).

[0067] In summation, the present invention provides novel compounds for use as steroid sulphatase inhibitors, and pharmaceutical compositions containing them.

[0068] The present invention will now be described only by way of example with reference to the accompanying drawings in which:-

Figure 1 shows the known structures of oestrone (1), oestrone sulphate (2), EMATE (3) and steroid sulphamates (4-5);

Figure 2 shows a compound of the Formula I;

Figure 3 shows a compound of the Formula II;

Figure 4 shows a compound of the Formula III;

Figure 5 shows a compound of the Formula IV;

Figure 6 shows a compound of the Formula V;

Figure 7 shows a compound of the Formula VI;

Figure 8 shows a compound of the Formula VII;

Figure 9 shows a compound of the Formula VIII;

Figure 10 shows a compound of the Formula IX;

Figure 11 shows a compound of the Formula X;

Figure 12 shows one embodiment of a method of preferring compounds of the present invention;

Figure 13 shows another embodiment of a method of preferring compounds of the present invention;

Figure 14 shows yet another embodiment of a method of preferring compounds of the present invention;

Figure 15 shows a further embodiment of a method of preferring compounds of the present invention;

Figure 16 shows a graph illustrating the *in vivo* inhibition of oestrone sulphatase by NOMATE (0.1 mg/Kg/day for five days); and

Figure 17 shows a graph illustrating the lack of effect of NOMATE (0.1 mg/Kg/day for five days) on uterine weights in ovariectomised rats.

[0069] The invention will now be described only by way of Examples.

Example 1- Preparative Methods

[0070] The preparation of various compounds in accordance with the present invention is illustrated in Figures 12 to 15. In these Figures, the curved lines attached to the phenyl rings represent the remainder of the ringed structure.

Example 1 - *In Vitro* Inhibition

[0071] The ability of compounds to inhibit oestrone sulphatase activity was assessed using either intact MCF-7 breast cancer cells or placental microsomes as previously described[11].

[0072] In this regard, the teachings of that earlier reference[11] are as follows:

Inhibition of Steroid Sulphatase Activity in MCF-7 cells by oestrone-3-sulphamate

[0073] Steroid sulphatase is defined as: Steryl Sulphatase EC 3.1.6.2.

[0074] Steroid sulphatase activity was measured *in vitro* using intact MCF-7 human breast cancer cells. This hormone dependent cell line is widely used to study the control of human breast cancer cell growth. It possesses significant steroid sulphatase activity (MacIndoe et al. *Endocrinology*, **123**, 1281-1287 (1988); Purohit & Reed, *Int. J. Cancer*, **50**, 901-905 (1992)) and is available in the U.S.A. from the American Type Culture Collection (ATCC) and in the U.K. (e. g. from The Imperial Cancer Research Fund). Cells were maintained in Minimal Essential Medium (MEM) (Flow Laboratories, Irvine, Scotland) containing 20 mM HEPES, 5% foetal bovine serum, 2 mM glutamine, non-essential amino acids and 0.075% sodium bicarbonate. Up to 30 replicate 25 cm^2 tissue culture flasks were seeded with approximately 1×10^5 cells/flask using the above medium. Cells were grown to 80% confluency and medium was changed every third day.

[0075] Intact monolayers of MCF-7 cells in triplicate 25 cm^2 tissue culture flasks were washed with Earle's Balanced Salt Solution (EBSS from ICN Flow, High Wycombe. U.K.) and incubated for 3-4 hours at 37°C with 5 pmol (7×10^5 dpm) [6,7-^{3}H]oestrone-3-sulphate (specific activity 60 Ci/mmol from New England Nuclear, Boston, Mass., U.S.A.) in serum-free MEM (2.5 ml) together with oestrone-3-sulphamate (11 concentrations: 0; 1fM; 0.01pM; 0.1pM; 1pM; 0.01nM; 0.1nM; 1nM; 0.01mM; 0.1mM; 1mM). After incubation each flask was cooled and the medium (1 ml) was pipetted into separate tubes containing [^{14}C]oestrone (7×10^3 dpm) (specific activity 97 Ci/mmol from Amersham International Radiochemical Centre, Amersham, U.K.). The mixture was shaken thoroughly for 30 seconds with toluene (5 ml). Experiments showed that >90% [^{14}C]oestrone and <0.1% [^{3}H]oestrone-3-sulphate was removed from the aqueous phase by this treatment. A portion (2 ml) of the organic phase was removed, evaporated and the ^{3}H and ^{14}C content of the residue determined by scintillation spectrometry. The mass of oestrone-3-sulphate hydrolysed was calculated from the ^{3}H counts obtained (corrected for the volumes of the medium and organic phase used, and for recovery of [^{14}C]oestrone added) and the specific activity of the substrate. Each batch of experiments included incubations of microsomes prepared from a sulphatase-positive human placenta (positive control) and flasks without cells (to assess apparent non-enzymatic hydrolysis of the substrate). The number of cell nuclei per flask was determined using a Coulter Counter after treating the cell monolayers with Zaponin. One flask in each batch was used to assess cell membrane

status and viability using the Trypan Blue exclusion method (Phillips, H.J. (1973) In: *Tissue culture and applications*, [eds: Kruse, D.F. & Patterson, M.K.]; pp. 406-408; Academic Press, New York).

[0076] Results for steroid sulphatase activity are expressed as the mean ± 1 S.D. of the total product (oestrone + oestradiol) formed during the incubation period (20 hours) calculated for 10^6 cells and, for values showing statistical significance, as a percentage reduction (inhibition) over incubations containing no oestrone-3-sulphamate. Unpaired Student's t-test was used to test the statistical significance of results.

Inhibition of Steroid Sulphatase Activity in Placental Microsomes by Oestrone-3-sulphamate

[0077] Sulphatase-positive human placenta from normal term pregnancies (Obstetric Ward, St. Mary's Hospital, London) were thoroughly minced with scissors and washed once with cold phosphate buffer (pH 7.4, 50 mM) then re-suspended in cold phosphate buffer (5 ml/g tissue). Homogenisation was accomplished with an Ultra-Turrax homogeniser, using three 10 second bursts separated by 2 minute cooling periods in ice. Nuclei and cell debris were removed by centrifuging (4°C) at 2000g for 30 minutes and portions (2 ml) of the supernatant were stored at -20°C. The protein concentration of the supernatants was determined by the method of Bradford (*Anal. Biochem.*, **72**, 248-254 (1976)).

[0078] Incubations (1 ml) were carried out using a protein concentration of 100 mg/ml, substrate concentration of 20 mM [6,7-^{3}H]oestrone-3-sulphate (specific activity 60 Ci/mmol from New England Nuclear, Boston, Mass., U.S.A.) and an incubation time of 20 minutes at 37°C. If necessary eight concentrations of compounds are employed: 0 (i.e. control); 0.05mM; 0.1mM; 0.2mM; 0.4mM; 0.6mM; 0.8mM; 1.0mM. After incubation each sample was cooled and the medium (1 ml) was pipetted into separate tubes containing [^{14}C]oestrone (7 x 10^3 dpm) (specific activity 97 Ci/mmol from Amersham International Radiochemical Centre, Amersham, U.K.). The mixture was shaken thoroughly for 30 seconds with toluene (5 ml). Experiments showed that >90% [^{14}C]oestrone and <0.1% [^{3}H]oestrone-3-sulphate was removed from the aqueous phase by this treatment. A portion (2 ml) of the organic phase was removed, evaporated and the ^{3}H and ^{14}C content of the residue determined by scintillation spectrometry. The mass of oestrone-3-sulphate hydrolysed was calculated from the ^{3}H counts obtained (corrected for the volumes of the medium and organic phase used, and for recovery of [^{14}C]oestrone added) and the specific activity of the substrate.

[0079] For the present invention, the percentage inhibition for the series of EMATE analogues tested in either MCF-7 cells or placental microsomes is shown in Table 1.

Example 2-*In Vivo* Studies

[0080] Using 17-deoxy oestrone-3-O-sulphamate (NOMATE, Figure 5, Formula IV where X = -OSO_2NH_2, Y = -CH_2- and R_1 and R_2 = H, and Figure 13) as a representative example, the ability of this compound to inhibit oestrone sulphatase activity *in vivo* was examined in rats. The oestrogenicity of this compound was examined in ovariectomised rats. In this model compounds which are oestrogenic stimulate uterine growth.

(i) Inhibition of oestrone sulphatase activity *in vivo*

[0081] NOMATE (0.1 mg/Kg/day for five days) was administered orally to rats with another group of animals receiving vehicle only (propylene glycol). At the end of the study samples of liver tissue were obtained and oestrone sulphatase activity assayed using ^{3}H oestrone sulphate as the substrate as previously described[11].

[0082] As shown in Figure 16, administration of this dose of NOMATE effectively inhibited oestrone sulphatase activity by 98% compared with untreated controls.

(ii) Lack of *in vivo* oestrogenicity

[0083] NOMATE (0.1 mg/Kg/day for five days) was administered orally to rats with another group of animals receiving vehicle only (propylene glycol). At the end of the study uteri were obtained and weighed with the results being expressed as uterine weight/whole body weight x 100.

[0084] As shown in Figure 17, administration of NOMATE at the dose tested, but had no significant effect on uterine growth, showing that at this dose the compound is not oestrogenic.

TABLE 1

Inhibition of Oestrone Sulphatase Activity in MCF-7 Cells or Placental Microsomes by EMATE Analogues			
Inhibitor	**Concentration Tested (mM)**	**% Inhibition (Mean)**	
		MCF-7 Cells	**Placental Microsomes**
2-n-propyl EMATE	0.1	41.1	-
	1	83.1	21.9
	10	92.2	43.2
	25	-	47.5
	50	-	61.1
	100	-	69.2
4-n-propyl EMATE	1	-	13.7
	10	-	10.2
	25	-	15.7
	50	-	16.3
	100	-	23.7
2,4-n-dipropyl EMATE	0.1	6.6	-
	1	10.6	-
2-allyl EMATE	0.01	23.2	-
	0.1	76.1	-
	1	94.2	45.6
	10	93.7	65.4
	25	-	75.3
	50	-	86.6
	100	-	89.6
4-allyl EMATE (approx 75%)	1	-	29.1
	10	-	54.2
	25	-	59.0
	50	-	65.1
	100	-	71.9
2,4-di-allyl EMATE	-	-	-
2-methoxy EMATE	0.1	96.0	-
	1	93.6	-
	10	96.2	99.0
	50	-	99.7
	100	-	99.7

TABLE 1 (continued)

Inhibition of Oestrone Sulphatase Activity in MCF-7 Cells or Placental Microsomes by EMATE Analogues			
Inhibitor	Concentration Tested (mM)	% Inhibition (Mean)	
		MCF-7 Cells	Placental Microsomes
2-nitro EMATE	0.05	-	44.5
	0.5	-	93.9
	5	-	99.0
	50	-	99.4
4-nitro EMATE	20	-	99.0
NOMATE (17-deoxy EMATE)	0.1	96.4	97.2
	1	99.1	99.5
	10	99.7	99.5
	25	99.7	99.7
- - = not tested - Irreversible time- and concentration-dependent inhibition is assumed for these compounds in keeping with established precedent[6].			

[0085] Other modifications of the present invention will be apparent to those skilled in the art.

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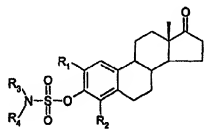
Claims

1. A sulphamate compound suitable for use as an inhibitor of oestrone sulphatase, wherein the compound is a sulphamate compound having Formula V;



Formula V

wherein

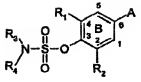
each of R_1 and R_2 is independently selected from H, alkyl, cycloalkyl, alkoxy, alkenyl, aryl, substituted alkyl, substituted cycloalkyl, substituted alkenyl, substituted aryl, a nitrogen containing group, a S containing group, or a carboxy containing group;

R_1 and R_2 may be the same or different but not both being H; and

each of R_3 and R_4 is independently selected from H, alkyl, cycloalkyl, alkenyl and aryl, wherein at least one of R_3 and R_4 is H.

2. A sulphamate compound suitable for use as an inhibitor of oestrone sulphatase, wherein the compound is a sulphamate compound having Formula II;

Formula II



wherein

R_1 is selected from alkyl, cycloalkyl, alkoxy, alkenyl, aryl, substituted alkyl, substituted cycloalkyl, substituted alkenyl, substituted aryl, a nitrogen containing group, a S containing group, or a carboxy containing group;

R_2 is selected from H, alkyl, cycloalkyl, alkoxy, alkenyl, aryl, substituted alkyl, substituted cycloalkyl, substituted alkenyl, substituted aryl, a nitrogen containing group, a S containing group, or a carboxy containing group;

R_1 and R_2 may be the same or different;

each of R_3 and R_4 is independently selected from H, alkyl, cycloalkyl, alkenyl and aryl, wherein at least one of R_3 and R_4 is H;

group A and ring B together are capable of mimicking the A and B rings of oestrone; and

group A is additionally attached to the carbon atom at position 1 of the ring B.

3. Use of a compound in the manufacture of a medicament to inhibit steroid sulphatase activity, wherein the compound is a sulphamate compound having Formula II;

Formula II

wherein

X is a sulphamate group;

R_1 is selected from alkyl, cycloalkyl, alkoxy, alkenyl, aryl, substituted alkyl, substituted cycloalkyl, substituted alkenyl, substituted aryl, a nitrogen containing group, a S containing group, or a carboxy containing group; and

R_2 is selected from H, alkyl, cycloalkyl, alkoxy, alkenyl, aryl, substituted alkyl, substituted cycloalkyl, substituted alkenyl, substituted aryl, a nitrogen containing group, a S containing group, or a carboxy containing group;

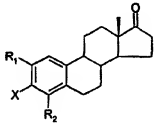
R_1 and R_2 may be the same or different;

wherein group A and ring B together are capable of mimicking the A and B rings of oestrone; and

wherein group A is additionally attached to the carbon atom at position 1 of the ring B.

4. Use of a compound in the manufacture of a medicament to inhibit steroid sulphatase activity, wherein the compound is a sulphamate compound having Formula V;

Formula V



wherein

X is a sulphamate group;

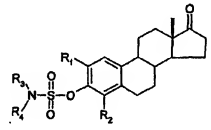
each of R_1 and R_2 is independently selected from H, alkyl, cycloalkyl, alkoxy, alkenyl, aryl, substituted alkyl,

substituted cycloalkyl, substituted alkenyl, substituted aryl, a nitrogen containing group, a S containing group, or a carboxy containing group; and

R_1 and R_2 may be the same or different but not both being H.

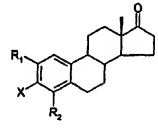
5. A sulphamate compound according to claim 2 wherein the compound has the Formula V

Formula V



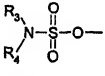
6. A use according to claim 3 wherein the compound has the Formula V

Formula V



7. A use according to claim 3,4 or 6 wherein the sulphamate group has the Formula III;

Formula III



wherein each of R_3 and R_4 is independently selected from H, alkyl, cycloalkyl, alkenyl and aryl, or together represent alkylene optionally containing one or more hetero atoms or groups in the alkylene chain.

8. A sulphamate compound or use according to claim 1, 2 or 7 whereIn at least one of R_3 and R_4 is H.

9. A sulphamate compound or use according to claim 8 wherein each of R_3 and R_4 is H.

10. A sulphamate compound or use according to one of claims 2, 3, 5 and 6 wherein
R_1 is selected from C_{1-6} alkyl, C_{1-6} cycloalkyl, C_{1-6} alkenyl, substituted C_{1-6} alkyl, substituted C_{1-6} cycloalkyl, substituted C_{1-6} alkenyl, substituted aryl, a nitrogen containing group, a S containing group, or a carboxy group having from 1-6 carbon atoms; and
R_2 is selected from H, C_{1-6} alkyl, C_{1-6} cycloalkyl, C_{1-6} alkenyl, substituted C_{1-6} alkyl, substituted C_{1-6} cycloalkyl, substituted C_{1-6} alkenyl, substituted aryl, a nitrogen containing group, a S containing group, or a carboxy group having from 1-6 carbon atoms.

11. A sulphamate compound or use according to claim 10 wherein
R_1 is selected from C_{1-6} alkyl, C_{1-6} alkenyl, a nitrogen containing group, or a carboxy group having from 1-6 carbon atoms; and

R_2 is selected from H, C_{1-6} alkyl, C_{1-6} alkenyl, a nitrogen containing group, or a carboxy group having from 1-6 carbon atoms.

12. A sulphamate compound or use according to claim 11 wherein
R_1 is selected from C_{1-6} alkyl, C_{1-6} alkenyl, NO_2, or a carboxy group having from 1-6 carbon atoms; and
R_2 is selected from H, C_{1-6} alkyl, C_{1-6} alkenyl, NO_2, or a carboxy group having from 1-6 carbon atoms.

13. A sulphamate compound or use according to claim 12 wherein
R_1 is selected from C_3 alkyl, C_3 alkenyl, NO_2, and H_3CO; and
R_2 is selected from H, C_3 alkyl, C_3 alkenyl, NO_2, and H_3CO.

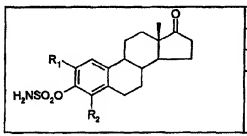
14. A sulphamate compound or use according to claim 1 or 4 wherein each of R_1 and R_2 is independently selected from H, C_{1-6} alkyl, C_{1-6} cycloalkyl, C_{1-6} alkenyl, substituted C_{1-6} alkyl, substituted C_{1-6} cycloalkyl, substituted C_{1-6} alkenyl, substituted aryl, a nitrogen containing group, a S containing group, or a carboxy group having from 1-6 carbon atoms.

15. A sulphamate compound or use according to claim 14 wherein each of R_1 and R_2 is independently selected from H, C_{1-6} alkyl, C_{1-6} alkenyl, a nitrogen containing group, or a carboxy group having from 1-6 carbon atoms.

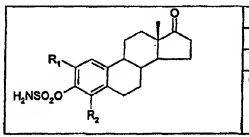
16. A sulphamate compound or use according to claim 15 wherein each of R_1 and R_2 is independently selected from H, C_{1-6} alkyl, C_{1-6} alkenyl, NO_2, or a carboxy group having from 1-6 carbon atoms.

17. A sulphamate compound or use according to claim 16 wherein each of R_1 and R_2 is independently selected from H, C_3 alkyl, C_3 alkenyl, NO_2, or H_3CO.

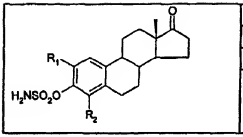
18. A sulphamate compound or use according to claim 1 wherein the compound is any one of the Formulae VI - IX.



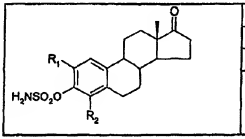
	R_1	R_2	Formula VI
a)	n-$CH_2CH_2CH_3$	H	
b)	H	n-$CH_2CH_2CH_3$	
c)	n-$CH_2CH_2CH_3$	n-$CH_2CH_2CH_3$	



	R_1	R_2	Formula VII
a)	-$CH_2CH{=}CH_2$	H	
b)	H	-$CH_2CH{=}CH_2$	
c)	-$CH_2CH{=}CH_2$	-$CH_2CH{=}CH_2$	



	R_1	R_2	Formula VIII
a)	H_3CO-	H	
b)	H	H_3CO-	
c)	H_3CO-	H_3CO-	



	R_1	R_2	Formula IX
a)	$-NO_2$	H	
b)	H	$-NO_2$	
c)	$-NO_2$	$-NO_2$	

19. A sulphamate compound or use according to any one of the preceding claims wherein the compound is further **characterised by** the feature that if the sulphamate group were to be substituted with a sulphate group to form a sulphate derivative, then the sulphate derivative would be hydrolysable by an enzyme having steroid sulphatase (E.C. 3.1.6.2) activity.

20. A sulphamate compound or use according to any one of claims 1 to 4 wherein R_1 and/or R_2 is an alkoxy group.

21. A sulphamate compound or use according to claim 20 wherein R_1 and/or R_2 is a methoxy group.

22. A sulphamate compound or use according to claim 20 wherein R_1 is an alkoxy group.

23. A sulphamate compound or use according to claim 22 wherein R_1 is a methoxy group.

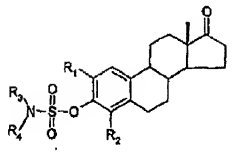
24. A sulphamate compound or use according to any one of claims 1 to 4 whereln R_1 and/or R_2 is an alkyl group.

25. A sulphamate compound or use according to claim 24 wherein R_1 and/or R_2 is a $C_{1\text{-}6}$ alkyl group.

26. A sulphamate compound or use according to claim 25 wherein R_1 and/or R_2 is an ethyl group.

Patentansprüche

1. Sulfamatverbindung, geeignet für die Verwendung als ein Inhibitor von Östronsulfatase, wobei die Verbindung eine Sulfamatverbindung ist, welche die Formel V aufweist,



Formel V

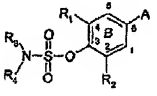
worin

R_1 und R_2 jeweils unabhängig voneinander unter H, Alkyl, Cycloalkyl, Alkoxy, Alkenyl, Aryl, substituiertem Alkyl, substituiertem Cycloalkyl, substituiertem Alkenyl, substituiertem Aryl, einer Stickstoff enthaltenden Gruppe, einer S enthaltenden Gruppe oder einer Carboxy enthaltenden Gruppe ausgewählt sind,

R_1 und R_2 gleich oder verschieden, aber nicht beide H sein können und

R_3 und R_4 jeweils unabhängig voneinander unter H, Alkyl, Cycloalkyl, Alkenyl und Aryl ausgewählt sind, wobei wenigstens eines von R_3 und R_4 H ist.

2. Sulfamatverbindung, geeignet für die Verwendung als ein Inhibitor von Östronsulfatase, wobei die Verbindung eine Sulfamatverbindung ist, welche die Formel II aufweist,



Formel II

worin

R_1 unter Alkyl, Cycloalkyl, Alkoxy, Alkenyl, Aryl, substituiertem Alkyl, substituiertem Cycloalkyl, substituiertem Alkenyl, substituiertem Aryl, einer Stickstoff enthaltenden Gruppe, einer S enthaltenden Gruppe oder einer Carboxy enthaltenden Gruppe ausgewählt ist,

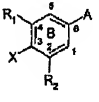
R_2 unter H, Alkyl, Cycloalkyl, Alkoxy, Alkenyl, Aryl, substituiertem Alkyl, substituiertem Cycloalkyl, substituiertem Alkenyl, substituiertem Aryl, einer Stickstoff enthaltenden Gruppe, einer S enthaltenden Gruppe oder einer Carboxy enthaltenden Gruppe ausgewählt ist,

R_1 und R_2 gleich oder verschieden sein können,

R_3 und R_4 jeweils unabhängig voneinander unter H, Alkyl, Cycloalkyl, Alkenyl und Aryl ausgewählt sind, wobei wenigstens eines von R_3 und R_4 H ist,

die Gruppe A und der Ring B zusammen in der Lage sind, die A- und B-Ringe von Östron nachzuahmen und die Gruppe A zusätzlich an das Kohlenstoffatom an Position 1 des Rings B gebunden ist.

3. Verwendung einer Verbindung bei der Herstellung eines Medikaments zur Hemmung von Steroidsulfataseaktivität, wobei die Verbindung eine Sulfamatverbindung ist, welche die Formel II aufweist,



Formel II

worin

X eine Sulfamatgruppe ist,

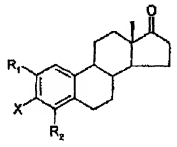
R_1 unter Alkyl, Cycloalkyl, Alkoxy, Alkenyl, Aryl, substituiertem Alkyl, substituiertem Cycloalkyl, substituiertem Alkenyl, substituiertem Aryl, einer Stickstoff enthaltenden Gruppe, einer S enthaltenden Gruppe oder einer Carboxy enthaltenden Gruppe ausgewählt ist,

R_2 unter H, Alkyl, Cycloalkyl, Alkoxy, Alkenyl, Aryl, substituiertem Alkyl, substituiertem Cycloalkyl, substituiertem Alkenyl, substituiertem Aryl, einer Stickstoff enthaltenden Gruppe, einer S enthaltenden Gruppe oder einer Carboxy enthaltenden Gruppe ausgewählt ist,

R_1 und R_2 gleich oder verschieden sein können,

die Gruppe A und der Ring B zusammen in der Lage sind, die A- und B-Ringe von Östron nachzuahmen und die Gruppe A zusätzlich an das Kohlenstoffatom an Position 1 des Rings B gebunden ist.

4. Verwendung einer Verbindung bei der Herstellung eines Medikaments zur Hemmung von Steroidsulfataseaktivität, wobei die Verbindung eine Sulfamatverbindung ist, welche die Formel V aufweist,



Formel V

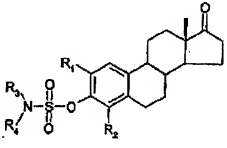
worin

X eine Sulfamatgruppe ist,

R_1 und R_2 jeweils unabhängig voneinander unter H, Alkyl, Cycloalkyl, Alkoxy, Alkenyl, Aryl, substituiertem Alkyl, substituiertem Cycloalkyl, substituiertem Alkenyl, substituiertem Aryl, einer Stickstoff enthaltenden Gruppe, einer S enthaltenden Gruppe oder einer Carboxy enthaltenden Gruppe ausgewählt sind, und

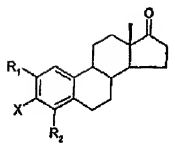
R_1 und R_2 gleich oder verschieden, aber nicht beide H sein können,

5. Sulfamatverbindung nach Anspruch 2, wobei die Verbindung die Formel V aufweist.



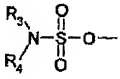
Formel V

6. Verwendung nach Anspruch 3, wobei die Verbindung die Formel V aufweist.



Formel V

7. Verwendung nach Anspruch 3,4 oder 6, wobei die Sulfamatgruppe die Formel III aufweist,



Formel III

worin R_3 und R_4 jeweils unabhängig voneinander unter H, Alkyl, Cycloalkyl, Alkenyl und Aryl ausgewählt sind oder zusammen Alkylen darstellen, welches wahlweise ein oder mehrere Heteroatome oder Gruppen in der Alkylenkette enthält.

8. Sulfamatverbindung oder Verwendung nach Anspruch 1, 2 oder 7, wobei wenigstens eines von R_3 und R_4 H ist.

9. Sulfamatverbindung oder Verwendung nach Anspruch 8, wobei R_3 und R_4 jeweils H sind.

10. Sulfamatverbindung oder Verwendung nach einem der Ansprüche 2, 3, 5 und 6, wobei
R_1 unter C_{1-6}-Alkyl, C_{1-6}-Cycloalkyl, C_{1-6}-Alkenyl, substituiertem C_{1-6}-Alkyl, substituiertem C_{1-6}-Cycloalkyl, substituiertem C_{1-6}-Alkenyl, substituiertem Aryl, einer Stickstoff enthaltenden Gruppe, einer S enthaltenden Gruppe oder einer Carboxygruppe mit 1-6 Kohlenstoffatomen ausgewählt ist und
R_2 unter H, C_{1-6}-Alkyl, C_{1-6}-Cycloalkyl, C_{1-6}-Alkenyl, substituiertem C_{1-6}-Alkyl, substituiertem C_{1-6}-Cycloalkyl, substituiertem C_{1-6}-Alkenyl, substituiertem Aryl, einer Stickstoff enthaltenden Gruppe, einer S enthaltenden Gruppe oder einer Carboxygruppe mit 1-6 Kohlenstoffatomen ausgewählt ist.

11. Sulfamatverbindung oder Verwendung nach Anspruch 10, wobei
R_1 unter C_{1-6}-Alkyl, C_{1-6}-Alkenyl, einer Stickstoff enthaltenden Gruppe oder einer Carboxygruppe mit 1-6 Kohlenstoffatomen ausgewählt ist und
R_2 unter H, C_{1-6}-Alkyl, C_{1-6}-Alkenyl, einer Stickstoff enthaltenden Gruppe oder einer Carboxygruppe mit 1-6 Kohlenstoffatomen ausgewählt ist.

12. Sulfamatverbindung oder Verwendung nach Anspruch 11, wobei
R_1 unter C_{1-6}-Alkyl, C_{1-6}-Alkenyl, NO_2 oder einer Carboxygruppe mit 1-6 Kohlenstoffatomen ausgewählt ist und
R_2 unter H, C_{1-6}-Alkyl, C_{1-6}-Alkenyl, NO_2 oder einer Carboxygruppe mit 1-6 Kohlenstoffatomen ausgewählt ist.

13. Sulfamatverbindung oder Verwendung nach Anspruch 12, wobei
R_1 unter C_3-Alkyl, C_3-Alkenyl, NO_2 und H_3CO ausgewählt ist und
R_2 unter H, C_3-Alkyl, C_3-Alkenyl, NO_2 und H_3CO ausgewählt ist.

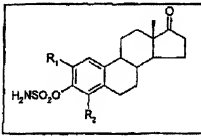
14. Sulfamatverbindung oder Verwendung nach Anspruch 1 oder 4, wobei R_1 und R_2 jeweils unabhängig voneinander unter H, C_{1-6}-Alkyl, C_{1-6}-Cycloalkyl, C_{1-6}-Alkenyl, substituiertem C_{1-6}-Alkyl, substituiertem C_{1-6}-Cycloalkyl, substituiertem C_{1-6}-Alkenyl, substituiertem Aryl, einer Stickstoff enthaltenden Gruppe, einer S enthaltenden Gruppe oder einer Carboxygruppe mit 1-6 Kohlenstoffatomen ausgewählt sind.

15. Sulfamatverbindung oder Verwendung nach Anspruch 14, wobei R_1 und R_2 jeweils unabhängig voneinander unter H, C_{1-6}-Alkyl, C_{1-6}-Alkenyl, einer Stickstoff enthaltenden Gruppe oder einer Carboxygruppe mit 1-6 Kohlenstoffatomen ausgewählt sind.

16. Sulfamatverbindung oder Verwendung nach Anspruch 15, wobei R_1 und R_2 jeweils unabhängig voneinander unter H, C_{1-6}-Alkyl, C_{1-6}-Alkenyl, NO_2 oder einer Carboxygruppe mit 1-6 Kohlenstoffatomen ausgewählt sind.

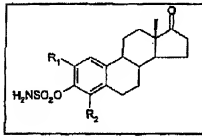
17. Sulfamatverbindung oder Verwendung nach Anspruch 16, wobei R_1 und R_2 jeweils unabhängig voneinander unter H, C_3-Alkyl, C_3-Alkenyl, NO_2 oder H_3CO ausgewählt sind.

18. Sulfamatverbindung oder Verwendung nach Anspruch 1, wobei die Verbindung eine der Formeln VI-IX aufweist.



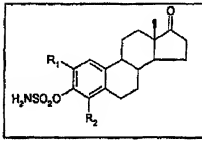
	R_1	R_2
a)	n-$CH_2CH_2CH_3$	H
b)	H	n-$CH_2CH_2CH_3$
c)	n-$CH_2CH_2CH_3$	n-$CH_2CH_2CH_3$

Formel VI



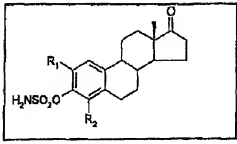
	R_1	R_2
a)	-$CH_2CH{=}CH_2$	H
b)	H	-$CH_2CH{=}CH_2$
c)	-$CH_2CH{=}CH_2$	-$CH_2CH{=}CH_2$

Formel VII



	R_1	R_2
a)	H_3CO-	H
b)	H	H_3CO-
c)	H_3CO-	H_3CO-

Formel VIII



	R_1	R_2	Formel IX
a)	$-NO_2$	H	
b)	H	$-NO_2$	
c)	$-NO_2$	$-NO_2$	

19. Sulfamatverbindung oder Verwendung nach einem der vorangegangenen Ansprüche, wobei die Verbindung weiter durch das Merkmal gekennzeichnet ist, daß, wenn die Sulfamatgruppe durch eine Sulfatgruppe unter Bildung eines Sulfatderivates substituiert wäre, dann das Sulfatderivat durch ein Enzym mit Steroidsulfatase (E.C. 3.1.6.2) -Aktivität hydrolysierbar wäre.

20. Sulfamatverbindung oder Verwendung nach einem der Ansprüche 1 bis 4, wobei R_1 und/oder R_2 eine Alkoxygruppe ist.

21. Sulfamatverbindung oder Verwendung nach Anspruch 20, wobei R_1 und/oder R_2 eine Methoxygruppe ist.

22. Sulfamatverbindung oder Verwendung nach Anspruch 20, wobei R_1 eine Alkoxygruppe ist.

23. Sulfamatverbindung oder Verwendung nach Anspruch 22, wobei R_1 eine Methoxygruppe ist.

24. Sulfamatverbindung oder Verwendung nach einem der Ansprüche 1 bis 4, wobei R_1 und/oder R_2 eine Alkylgruppe ist.

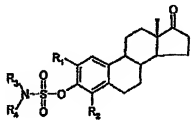
25. Sulfamatverbindung oder Verwendung nach Anspruch 24, wobei R_1 und/oder R_2 eine C_{1-6}-Alkylgruppe ist.

26. Sulfamatverbindung oder Verwendung nach Anspruch 25, wobei R_1 und/oder R_2 eine Ethylgruppe ist.

Revendications

1. Composé consistant en sulfamate convenable pour l'utilisation comme inhibiteur d'oestrone-sulfatase, ledit composé étant un sulfamate répondant à la formule V ;

Formule V



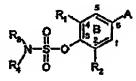
dans laquelle

chacun des groupes R_1 et R_2 est choisi indépendamment entre H, des groupes alkyle, cycloalkyle, alkoxy, alcényle, aryle, alkyle substitué, cycloalkyle substitué, alcényle substitué, aryle substitué, un groupe contenant de l'azote, un groupe contenant S ou un groupe à fonction carboxy ;

R_1 et R_2 peuvent être identiques ou différents mais ne représentent pas l'un et l'autre H ; et

chacun des groupes R_3 et R_4 est choisi indépendamment entre H, des groupes alkyle, cycloalkyle, alcényle et aryle, au moins un des groupes R_3 et R_4 représentant H.

2. Composé consistant en sulfamate convenable pour l'utilisation comme inhibiteur d'oestrone-sulfatase, ledit composé étant un sulfamate répondant à la formule II :



Formule II

dans laquelle

R_1 est choisi entre des groupes alkyle, cycloalkyle, alkoxy, alcényle, aryle, alkyle substitué, cycloalkyle substitué, alcényle substitué, aryle substitué, un groupe contenant de l'azote, un groupe contenant S ou un groupe à fonction carboxy ;

R_2 est choisi entre H, des groupes alkyle, cycloalkyle, alkoxy, alcényle, aryle, alkyle substitué, cycloalkyle substitué, alcényle substitué, aryle substitué, un groupe contenant de l'azote, un groupe contenant S ou un groupe à fonction carboxy ;

R_1 et R_2 peuvent être identiques ou différents ;

chacun des groupes R_3 et R_4 est choisi indépendamment entre H, des groupes alkyle, cycloalkyle, alcényle et aryle, au moins un des groupes R_3 et R_4 représentant H.

le groupe A et le noyau B, conjointement, sont capables de mimer les noyaux A et B de l'oestrone ; et

le groupe A est fixé en outre à l'atome de carbone en position 1 du noyau B.

3. Utilisation d'un composé dans la production d'un médicament destiné à inhiber l'activité de stéroïde-sulfatase, dans laquelle le composé est un sulfamate répondant à la formule II:

Formule II

dans laquelle

X représente un groupe sulfamate ;

R_1 est choisi entre des groupes alkyle, cycloalkyle, alkoxy, alcényle, aryle, alkyle substitué, cycloalkyle substitué, alcényle substitué, aryle substitué, un groupe contenant de l'azote, un groupe contenant S ou un groupe à fonction carboxy ; et

R_2 est choisi entre H, des groupes alkyle, cycloalkyle, alkoxy, alcényle, aryle, alkyle substitué, cycloalkyle substitué, alcényle substitué, aryle substitué, un groupe contenant de l'azote, un groupe contenant S ou un groupe à fonction carboxy ;

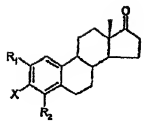
R_1 et R_2 peuvent être identiques ou différents ;

le groupe A et le noyau B, conjointement, sont capables de mimer les noyaux A et B de l'oestrone ; et

le groupe A est fixé en outre à l'atome de carbone en position 1 du noyau B.

4. Utilisation d'un composé dans la production d'un médicament destiné à inhiber l'activité de stéroïde-sulfatase, dans laquelle le composé est un sulfamate répondant à la formule V :

Formule V



dans laquelle

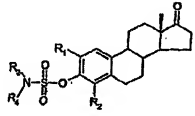
X représente un groupe sulfamate ;

chacun des groupes R_1 et R_2 est choisi indépendamment entre H, des groupes alkyle, cycloalkyle, alkoxy, alcényle, aryle, alkyle substitué, cycloalkyle substitué, alcényle substitué, aryle substitué, un groupe contenant de l'azote, un groupe contenant S ou un groupe à fonction carboxy ; et

R_1 et R_2 peuvent être identiques ou différents mais ne représentent pas l'un et l'autre H.

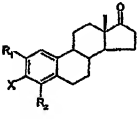
5. Composé consistant en sulfamate suivant la revendication 2, qui répond à la formule V

Formule V



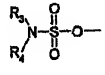
6. Utilisation suivant la revendication 3, dans laquelle le composé répond à la formule V

Formule V



7. Utilisation suivant la revendication 3, 4 ou 6, dans laquelle le groupe sulfamate répond à la formule III

Formule III



dans laquelle chacun des groupes R3 et R4 est choisi indépendamment entre H, des groupes alkyle, cycloalkyle, alcényle et aryle, ou bien ces groupes, conjointement, représentent un groupe alkylène contenant facultativement un ou plusieurs hétéro-atomes ou groupes hétéro-atomiques dans la chaîne alkylène.

8. Composé consistant en sulfamate ou utilisation suivant la revendication 1, 2 ou 7, dans lequel au moins un des groupes R_3 et R_4 représente H.

9. Composé consistant en sulfamate ou utilisation suivant la revendication 8, dans lequel chacun des groupes R_3 et R_4 représente H.

10. Composé consistant en sulfamate ou utilisation suivant une des revendications 2, 3, 5 et 6, dans lequel
R_1 est choisi entre des groupes alkyle en C_1 à C_8, cycloalkyle en C_1 à C_8, alcényle en C_1 à C_6, alkyle en C_1 à C_6 substitué, cycloalkyle en C_1 à C_6 substitué, alcényle en C_1 à C_6 substitué, aryle substitué, un groupe contenant de l'azote, un groupe contenant S ou un groupe carboxy ayant 1 à 6 atomes de carbone ; et
R_2 est choisi entre H, des groupes alkyle en C_1 à C_8, cycloalkyle en C_1 à C_8, alcényle en C_1 à C_6, alkyle en C_1 à C_6 substitué, cycloalkyle en C_1 à C_6 substitué, alcényle en C_1 à C_6 substitué, aryle substitué, un groupe contenant de l'azote, un groupe contenant S et un groupe carboxy ayant 1 à 6 atomes de carbone.

11. Composé consistant en sulfamate ou utilisation suivant la revendication 10, dans lequel
R_1 est choisi entre des groupes alkyle en C_1 à C_6, alcényle en C_1 à C_6, un groupe contenant de l'azote et un groupe carboxy ayant 1 à 6 atomes de carbone ; et
R_2 est choisi entre H, des groupes alkyle en C_1 à C_6, alcényle en C_1 à C_6, un groupe contenant de l'azote ou un groupe carboxy ayant 1 à 6 atomes de carbone.

12. Composé consistant en sulfamate ou utilisation suivant la revendication 11, dans lequel
R_1 est choisi entre des groupes alkyle en C_1 à C_8, alcényle en C_1 à C_8, NO_2, ou un groupe carboxy ayant 1 à 6 atomes de carbone ; et
R_2 est choisi entre H, des groupes alkyle en C_1 à C_8, alcényle en C_1 à C_8, NO_2, ou un groupe carboxy ayant 1 à 6 atomes de carbone.

13. Composé consistant en sulfamate ou utilisation suivant la revendication 12, dans lequel
R_1 est choisi entre des groupes alkyle en C_3, alcényle, NO_2 et H_3CO ; et
R_2 est choisi entre H, des groupes alkyle en C_3, alcényle en C_3, NO_2 et H_3CO.

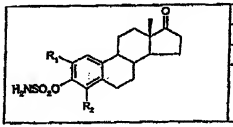
14. Composé consistant en sulfamate ou utilisation suivant la revendication 1 ou 4, dans lequel chacun des groupes R_1 et R_2 est choisi indépendamment entre H, des groupes alkyle en C_1 à C_8, cycloalkyle en C_1 à C_8, alcényle en C_1 à C_6, alkyle en C_1 à C_6 substitué, cycloalkyle en C_1 à C_6 substitué, alcényle en C_1 à C_6 substitué, aryle substitué, un groupe contenant de l'azote, un groupe contenant S ou un groupe carboxy ayant 1 à 6 atomes de carbone.

15. Composé consistant en sulfamate ou utilisation suivant la revendication 14, dans lequel chacun des groupes R_1 et R_2 est choisi indépendamment entre H, des groupes alkyle en C_1 à C_6, alcényle en C_1 à C_6, un groupe contenant de l'azote ou un groupe carboxy ayant 1 à 6 atomes de carbone.

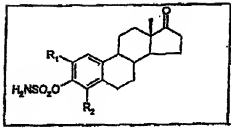
16. Composé consistant en sulfamate ou utilisation suivant la revendication 15, dans lequel chacun des groupes R_1 et R_2 est choisi indépendamment entre H, des groupes alkyle en C_1 à C_6, alcényle en C_1 à C_6, NO_2, ou un groupe carboxy ayant 1 à 6 atomes de carbone.

17. Composé consistant en sulfamate ou utilisation suivant la revendication 16, dans lequel chacun des groupes R_1 et R_2 est choisi indépendamment entre H, des groupes alkyle en C_3, alcényle en C_3, NO_2 et H_3CO.

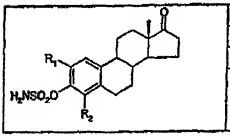
18. Composé consistant en sulfamate ou utilisation suivant la revendication 1, qui est l'un quelconque des composés de formules VI à IX



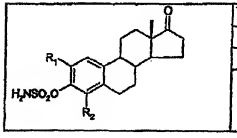
	R_1	R_2	Formule VI
a)	n-$CH_2CH_2CH_3$	H	
b)	H	n-$CH_2CH_2CH_3$	
c)	n-$CH_2CH_2CH_3$	n-$CH_2CH_2CH_3$	



	R_1	R_2	Formule VII
a)	$-CH_2CH=CH_2$	H	
b)	H	$-CH_2CH=CH_2$	
c)	$-CH_2CH=CH_2$	$-CH_2CH=CH_2$	



	R_1	R_2	Formule VIII
a)	H_3CO-	H	
b)	H	H_3CO-	
c)	H_3CO-	H_3CO-	



	R_1	R_2	Formule IX
a)	$-NO_2$	H	
b)	H	$-NO_2$	
c)	$-NO_2$	$-NO_2$	

19. Composé consistant en sulfamate ou utilisation suivant l'une quelconque des revendications précédentes, dans lequel le composé est **caractérisé en outre par le fait que**, si le groupe sulfamate devait être substitué par un groupe sulphate pour former un dérivé consistant en sulphate, alors le dérivé consistant en sulphate serait hydrolysable par une enzyme ayant une activité de stéroïde-sulfatase (E.C. 3.1.6.2).

20. Composé consistant en sulfamate ou utilisation suivant l'une quelconque des revendications 1 à 4, dans lequel R_1 et/ou R_2 représente un groupe alkoxy.

21. Composé consistant en sulfamate ou utilisation suivant la revendication 20, dans lequel R_1 et/ou R_2 représente un groupe méthoxy.

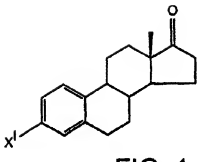
22. Composé consistant en sulfamate ou utilisation suivant la revendication 20, dans lequel R_1 représente un groupe alkoxy.

23. Composé consistant en sulfamate ou utilisation suivant la revendication 22, dans lequel R_1 représente un groupe méthoxy.

24. Composé consistant en sulfamate ou utilisation suivant l'une quelconque des revendications 1 à 4, dans lequel R_1 et/ou R_2 représente un groupe alkyle.

25. Composé consistant en sulfamate ou utilisation suivant la revendication 24, dans lequel R_1 et/ou R_2 représente un groupe alkyle en C_1 à C_6.

26. Composé consistant en sulfamate ou utilisation suivant la revendication 25, dans lequel R_1 et/ou R_2 représente un groupe éthyle.

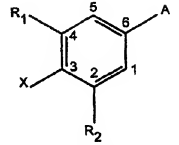


X^I	
(1)	-OH
(2)	$-OSO_3^-$
(3)	$-OSO_2NH_2$
(4)	$-NHSO_2NH_2$
(5)	$-SSO_2NH_2$

FIG. 1

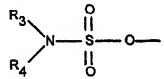
X - B - A I

FIG. 2



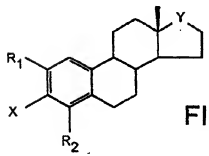
II

FIG. 3



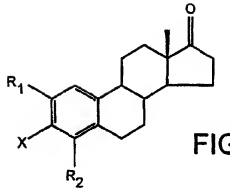
III

FIG. 4



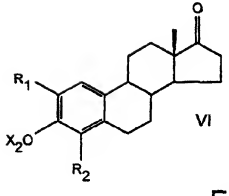
IV

FIG. 5



V

FIG. 6

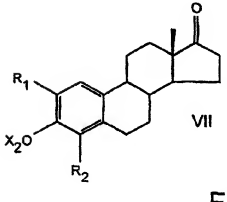


VI

X_2 = - SO_2NH_2

	R_1	R_2
a)	n-$CH_2CH_2CH_3$	H
b)	H	n-$CH_2CH_2CH_3$
c)	n-$CH_2CH_2CH_3$	n-$CH_2CH_2CH_3$

FIG. 7

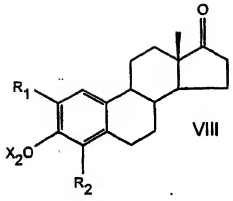


VII

X_2 = - SO_2NH_2

	R_1	R_2
a)	-$CH_2CH=CH_2$	H
b)	H	-$CH_2CH=CH_2$
c)	-$CH_2CH=CH_2$	-$CH_2CH=CH_2$

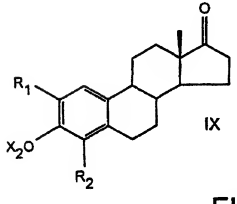
FIG. 8



X_2 = - SO_2NH_2

	R_1	R_2
a)	H_3CO-	H
b)	H	H_3CO-
c)	H_3CO-	H_3CO-

FIG. 9



X_2 = - SO_2NH_2

	R_1	R_2
a)	$-NO_2$	H
b)	H	$-NO_2$
c)	$-NO_2$	$-NO_2$

FIG. 10

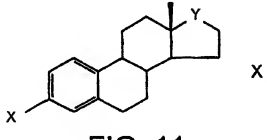
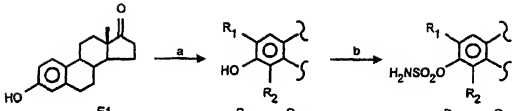


FIG. 11



	R_1	R_2
(1)	NO_2	H
(2)	H	NO_2

	R_1	R_2
(3)	NO_2	H
(4)	H	NO_2

FIG. 12

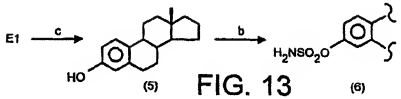
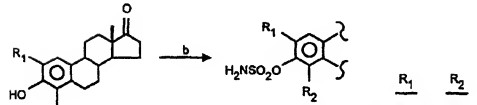


FIG. 13



	R_1	R_2
(7)	MeO	H
(8)	H	MeO

FIG. 14

	R_1	R_2
(9)	MeO	H
(10)	H	MeO

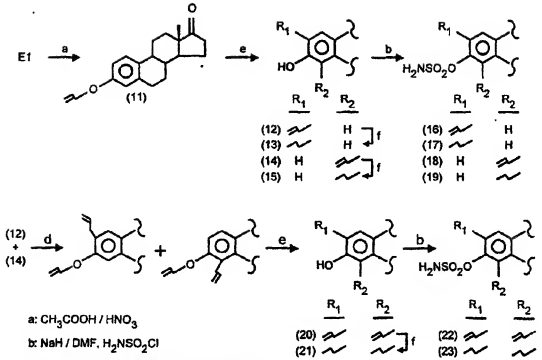

E1
a
(11)
e
b
R1
R2
HO
H2NSO2O
(12) H
(13)
(14) H
(15) H
(16)
(17)
(18) H
(19) H
f
(12)
+
(14)
d
(20)
(21)
(22)
(23)
a: CH3COOH / HNO3
b: NaH / DMF, H2NSO2Cl
c: NH2NH2·H2O, KOH / DIETHYLENE GLYCOL
d: NaH / DMF, Br
e: N, N-DIETHYLANILINE, Δ
f: Pd/C, H2

FIG. 15

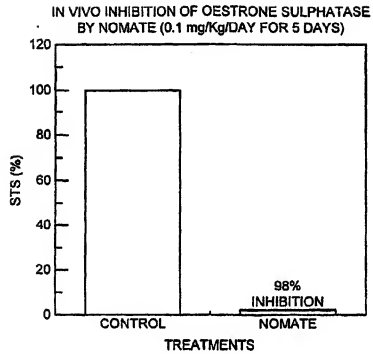

IN VIVO INHIBITION OF OESTRONE SULPHATASE
BY NOMATE (0.1 mg/Kg/DAY FOR 5 DAYS)
120
100
80
60
40
20
0
STS (%)
98%
INHIBITION
CONTROL
NOMATE
TREATMENTS

FIG. 16

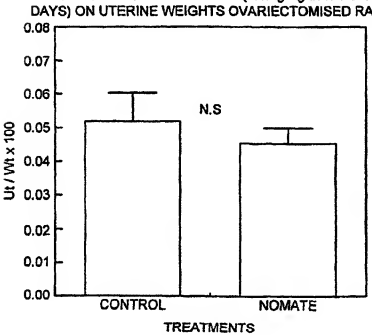

LACK OF EFFECT OF NOMATE (0.1mg/Kg/DAY FOR 5
DAYS) ON UTERINE WEIGHTS OVARIECTOMISED RATS
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
Ut / Wt x 100
N.S
CONTROL
NOMATE
TREATMENTS

FIG. 17